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EXPERIMENTAL HUMAN SCURVY*

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BOSTON

ALTHOUGH thoroughly investigated in the guinea pig,[1-4] experimental scurvy has not been studied in the human adult. Indeed, until recently there seemed little to warrant such a study. The numerous and widespread clinical reports of scorbutus dating back to Hippocrates[5-7] have drawn a detailed and comprehensive picture of the disease. With the discovery of other vitamins and the isolation of vitamin C, however, the question arises as to what roles such factors as multiple avitaminosis and infection may have played in the syndrome of scurvy and its complications. Obviously the vast majority of cases comprising the literature of this subject involve not only vitamin C deficiency but also multiple subclinical avitaminosis as well; and in many cases infection is an additional complicating factor. Moreover, with the recent development of methods for the determination of ascorbic acid in the blood and urine,[8-12] the necessity has arisen for correlating various blood and urine levels with degrees of pure vitamin C deficiency uncomplicated by other factors.

How long, for example, does it take for an adult on a diet entirely deficient in only vitamin C to become scorbutic? The crews of seventeenth-century and eighteenth-century sailing vessels, having rations undoubtedly poor in many vitamins, frequently developed signs of scurvy after sixty to one hundred and twenty days at sea.[13] Stark,[14] in 1769, produced scorbutus and also some symptoms of vitamin B deficiency in himself by subsisting on a diet of bread and water for ten weeks, an effort which later resulted in his death.

In other communications[15, 16] we have presented partial data concerning an adult male on a diet totally deficient in vitamin C, but supplemented by all the other known vitamins. We now present the completed experiment in detail, representing six months of total vitamin C deficiency. To our knowledge, no controlled vitamin C deficiency has previously been carried longer than twelve days,[17] although Van Eekelen[18] remained on an uncontrolled vitamin C deficient diet for eighty-four days.

EXPERIMENTAL DATA

J. H. C., a male adult weighing one hundred and fifty-eight pounds, with a negative history, physical examination and laboratory findings, placed himself on a diet containing no milk and no fruit or vegetables of any kind.||

Daily plasma determinations were done, using the macromethod of Mindlin and Butler,[9] and frequent plasma determinations, which checked with ours, were also done by Dr. Allan M. Butler and Miss Margaret Cushman of the Children's Hospital. The latter, who have developed a new method for determining the vitamin C in the white-cell-platelet layer of centrifuged blood,[10] also did such determinations at frequent intervals.

In Figure 1 it will be seen that the plasma vitamin C fell irregularly but rapidly, reaching zero after forty-one days of the diet. It remained at zero constantly thereafter. Between the one hundred and sixty-fourth and the one hundred and seventy-first day of the diet, during which time the subject visited Chicago, daily plasma determinations were done by the Farmer and Abt titration method[8] at the Illinois Research Hospital, through the courtesy of Dr. Henry G. Poncher. A microdetermination was also done by Dr. Chester J. Farmer, using his own method, at Northwestern University. All these determinations gave zero readings.

The white-cell-platelet ascorbic acid, as determined by Butler and Cushman by their own method, fell gradually from a relatively normal level of 28 mg. per 100 cc. on the seventeenth day of the diet to 4 mg. per 100 cc. on the eighty-second day, after which the level remained at zero.

*From the Fifth Surgical Service and the Surgical Research Laboratory, Boston City Hospital, the Department of Surgery, Harvard Medical School, and the Fatigue Laboratory, Harvard School of Business Administration. This work was aided by anonymous donors and Hoffman-La Roche, Inc., Nutley, New Jersey. Assistance in securing the data was in part furnished by the personnel of the Work Projects Administration (Project 17580).

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||For the first two months well-cooked meat (not over 200 gm. per day) and small amounts of cream were allowed, but thereafter all meat and cream were also omitted. For the last four months the diet consisted of cheese (Swiss and American), bread, crackers, eggs, beer (not over 1500 cc. per week), black coffee and a standard brand of pure chocolate candy, consisting only of chocolate bean and sugar, roasted and processed at 215°F. for seventy-two hours. During the entire dietary period the subject received daily 30,000 international units of vitamin A, 132 international units of vitamin B_1, and 80 microgm. of riboflavin, fortified by 10 Harris yeast tablets, 50 mg. nicotinic acid, 5280 international units of vitamin D and, after the second month, 4 cc. of wheat-germ oil.

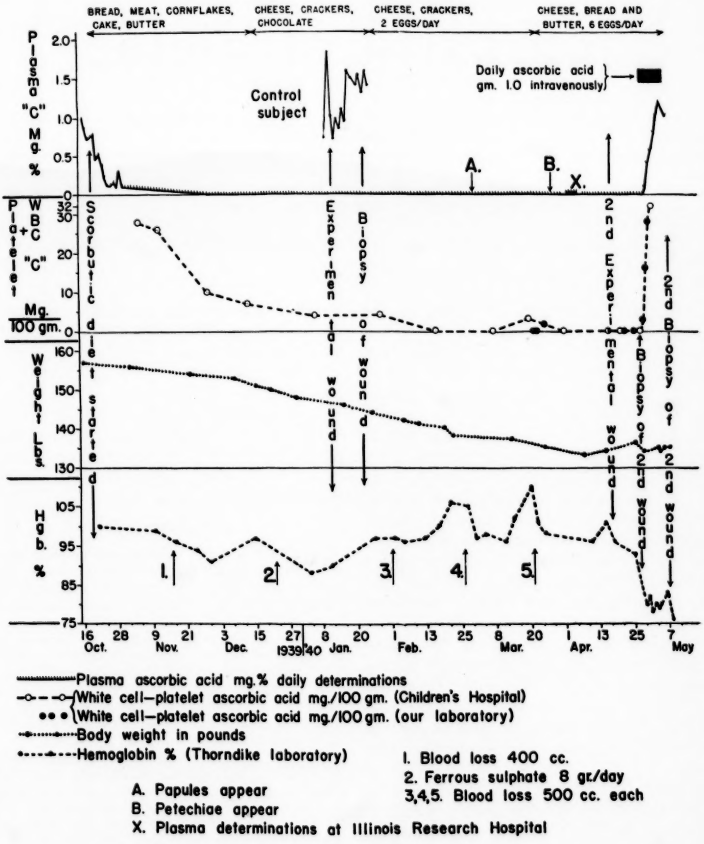
BREAD, MEAT, CORNFLAKES, CAKE, BUTTER
CHEESE, CRACKERS, CHOCOLATE
CHEESE, CRACKERS, 2 EGGS/DAY
CHEESE, BREAD AND BUTTER, 6 EGGS/DAY
Plasma "C" Mg. %
Control subject
Daily ascorbic acid gm. 1.0 intravenously
A.
B.
X.
Platelet WBC "C" Mg. 100 gm.
Scorbutic
Experimental wound
Biopsy of wound
2nd Experimental wound
Biopsy of 2nd wound
2nd Biopsy of 2nd wound
Weight Lbs.
Diet start
Hgb. %
1.
2.
3.
4.
5.
16 Oct. 28 9 Nov. 21 3 Dec. 15 27 8 1939/40 Jan. 20 1 Feb. 13 25 8 Mar. 20 1 Apr. 13 25 7 May
Plasma ascorbic acid mg.% daily determinations
White cell—platelet ascorbic acid mg./100 gm. (Children's Hospital)
White cell—platelet ascorbic acid mg./100 gm. (our laboratory)
Body weight in pounds
Hemoglobin % (Thorndike laboratory)
1. Blood loss 400 cc.
2. Ferrous sulphate 8 gr./day
3,4,5. Blood loss 500 cc. each
A. Papules appear
B. Petechiae appear
X. Plasma determinations at Illinois Research Hospital

FIGURE 1. *Graph of Pertinent Data in a Case of Experimental Human Scurvy.*

ADDITIONAL DATA

Vitamin C Content of Plasma (mg. per 100 cc.):* (17)† 0.2; (23) 0.1; (41) 0.0; (55) 0.0; (79) 0.0; (87) 0.0; (100) 0.0; (121) 0.0; (135) 0.0; (153) 0.0; (181) 0.0; (185) 0.0; (192) 0.0.

Vitamin C Content of Whole Blood (mg. per 100 cc.):* (17) 0.2; (23) 0.1; (41) 0.1; (79) 0.1; (87) 0.0; 0.0 thereafter, as plasma above.

Basal Metabolic Rate (per cent): (1) +11.5; (7) +5.1; (10) +0.9; (13) –12.5; (17) –12.6; (23) –10.7; (30) –5.0; (36) –8.7; (44) –6.2; (48) –14.1; (51) –16.6; (59) –6.4; (70) –20.0; (77) –21.0; (82) –19.6; (89) –9.2; (93) –13.6; (105) –10.3; (110) –10.0; (114) –15.4; (118) –11.0; (133) –8.3; (139) –17.0; (150) –15.9; (156) –15.9; (161) –22.0; (175) –21.8; (181) –17.4; (187) –6.4; thereafter see Table 3.

Red-Cell Count (millions): (0) 5.0; (5) 5.0; (12) 5.0; (23) 5.0; (29) donor for transfusion, 400 cc.; (30) 4.6; (37) 4.2; (42) 4.5; (57) 4.8; (77) 4.3; (85) 4.5; (102) 5.0; (106) donor for transfusion, 500 cc.; (110) 4.9; (122) 5.5; (124) 5.6; (131) donor for transfusion, 500 cc.; (132) 5.3; (138) 5.1; (148) 5.4; (156) 5.2; (158) acute blood loss, 500 cc.; (159) 5.2; (175) 5.2; (185) 5.2; (190) 4.8; ‡; (194) 4.2; (195) 4.3; (196) 4.2; (197) 4.3; (198) 4.3; (201) 4.2;(203) 3.8; (205) 4.3; (209) 4.5.

White-Cell Count (thousands): (0) 4.7; (57) 4.8; (85) 4.5; (102) 4.2; (124) 4.3; (132) 3.5; (138) 4.4; (156) 3.2; (175) 3.4; (180) 3.6; ‡; (193) 5.0; (195) 4.7; (197) 3.7; (198) 5.4; (201) 9.0; (205) 6.0.

During the first four months of the deficient diet all physical findings were negative. There was a slight fall in weight and basal metabolic rate and a feeling of easy fatigability and slight weakness (see below).

tion of hairs. These lesions, which progressed in severity during the ensuing three weeks, resembled a mild form of the lesion described as typical of vitamin A deficiency.[19] Each papule contained an ingrown hair, which could be

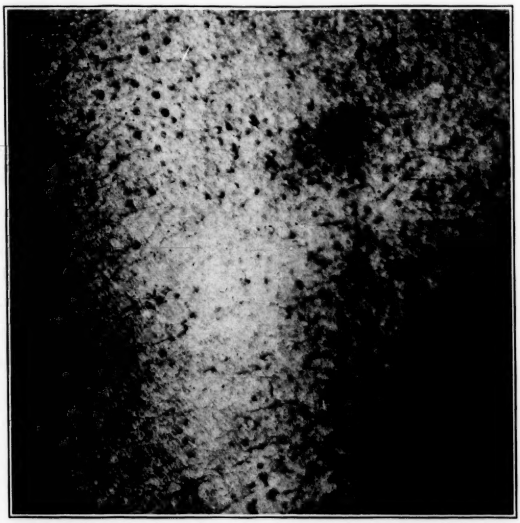

FIGURE 2. *Lateral View of the Thigh after Five and a Half Months of Vitamin C-Free Diet.*
Note the hyperkeratotic papules surrounding the hair follicles.

After one hundred and thirty-four days had elapsed, small perifollicular hyperkeratotic papules began to develop over the buttocks and the posterior aspects of the calves (Figs. 2 and 3). There was noticeable fragmenta-

seen if the hyperkeratotic plug was picked or scraped off, leaving a small, slightly bleeding crater. Associated with these papules was a marked dryness of the skin, particularly over the extensor surfaces, and the backs

ADDITIONAL DATA (*continued*)

Differential White-Cell Count (per cent): (76) 70 P, 26 L, 2 M, 1 E, 1 B; (132) 55 P, 38 L, 4 M, 1 E, 1 B; (180) 60 P, 24 L, 13 M, 2 E, 1 B; ‡ ; (204) 66 P, 23 L, 8 M, 2 E, 1 B.
Hematocrit: (0) 0.48; (77) 0.50; (87) 0.49; (107) 0.45; (122) 0.45; (122) 0.47; (154) 0.48; (180) 0.46; ‡ ; (194) 0.39; (198) 0.38; (203) 0.36; (205) 0.41.
Sedimentation Rate (mm. per minute): (28) 0.4; (75) 0.01; (93) 0.03; (111) 0.05; (145) 0.2; (178) 0.1; (191) 0.2.
Blood Sodium (milliequiv. per liter): (33) 142; (43) 136; (78) 143; (89) 147; (122) 149; (146) 137; (187) 136; ‡ ; (198) 143.
Blood Complement: normal titer throughout (78, 121, 152, 190).
Göthlin Test: negative throughout (36, 53, 67, 88, 105, 110, 120, 129, 134, 145, 160, 170, 192).
Bleeding Time (Ivy, seconds): (71) 124; (102) 290; (122) 190; (149) 182; (178) 110; (187) 125.
Clotting Time (Ivy, minutes): (71) 9; (102) 8; (122) 12; (149) 10; (187) 6.
Guaiac Test on Stool: negative throughout (54, 95, 120, 139, 145, 192).
Urine (sugar, albumin and sediment): normal throughout (0, 55, 120, 130, 188, 192).
Serum Protein (gm. per 100 cc.): (93) 6.5, A:G as 4.3:2.2; (121) 5.0; (154) 6.5; (187) 7.1.
Chest X-Ray Film: normal throughout (0, 46, 85, 112, 146, 177).
Electrocardiogram: normal throughout (35, 85, 112, 146, 177).
Red-Cell Fragility Test: (156) normal.

*Determinations at the Children's Hospital (Boston) Laboratory.
†Numbers in parentheses refer to days of diet.
‡Vitamin C therapy started on the one hundred and ninety-second day of the diet.

of the hands became markedly roughened, the pores standing out in exaggerated fashion. The similarity between the lesions of vitamin A deficiency and those of vitamin C deficiency has been previously point out.[20, 21] In order to determine the presence or absence of vitamin A deficiency a biophotometric test [22] was done by Dr. Harold J. Jeghers, of the Boston City Hospital. This showed perfectly normal visual adaptation in the dark. At the same time vitamin A determinations done on the plasma were within normal limits, both in our laboratory and that at the Children's Hospital. These findings, coupled with the fact that at least 30,000 international units of vitamin A had been taken daily, — the normal requirement being only 5000 units,[22] — seem to us to rule out vitamin A deficiency as a possible cause for these lesions.

After one hundred and sixty-one days of the diet, the plasma ascorbic acid having been zero for one hundred and twenty days, there appeared for the first time small perifollicular hemorrhages or petechiae over the lower legs (Fig. 4). These lesions did not fade on pressure and were not elevated. They seemed to occur in greatest numbers after the subject had been standing for some time (five hours), appearing for the first time, in fact, following a long period of operating. First seen over the inner and extensor aspects of the lower legs, the petechiae crept upward as the experiment progressed, until at the end of six months they were abundant over the lower thighs, where they seemed to take the place of the hyperkeratotic lesions already described.

Following the administration of vitamin C all skin lesions rapidly cleared (Fig. 5).

Wound Healing

At the end of three months, after the plasma ascorbic acid had been zero for forty-four days, a sizable wound was made in the right mid-back of the subject. Ten days later biopsy of this wound showed good healing, as compared with a normal control[15]; histological study showed ample intercellular substance and capillary formation (Fig. 6). At the end of one hundred and eighty-two days, after the plasma ascorbic acid had been at zero for one hundred and forty-one days, the white-cell-platelet ascorbic acid at zero for sixty-one days, and the petechiae apparent over the lower limbs for twenty-one days, a similar wound was made in the left mid-back.*

The skin sutures were removed on the sixth postoperative day, at which time the wound seemed to be progressing normally.

On the tenth postoperative day, under Pentothal anesthesia, a biopsy was made of the wound through an incision transverse to it and again extending down to the sacrospinalis muscle. Beneath the skin, which appeared well healed, there was no healing of the wound, which was filled with unorganized blood clot (Fig. 7). This was in marked contradistinction to the findings at three months, when there was perfect wound healing. So little healing had occurred that it was necessary to insert a small rubber drain, and the wound was brought together only with silk sutures through skin and subcutaneous tissue.

Sections of this wound, examined by Dr. Frederick Parker, Jr., of the Boston City Hospital, and Dr. S. Burt

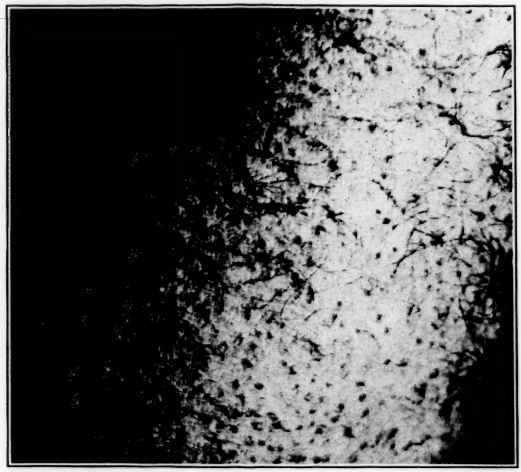

FIGURE 3. *Posterior View of the Thigh after Five and a Half Months of Vitamin C-Free Diet.*
Note the fragmentation of the hairs.

*A 6-cm. transverse incision was made in the left mid-back under local anesthesia (1 per cent novocain). The latissimus dorsi aponeurosis was divided in the plane of its fibers and the anterior sacrospinalis fascia divided, revealing the sacrospinalis muscle, 1 to 2 gm. of which was removed. The sacrospinalis fascia was then closed with interrupted mattress sutures of plain No. 00 catgut. Considerable difficulty was experienced in approximating the edges of this fascia, the sutures tearing out with great ease. (No such difficulty had been encountered at the previous operation.) The latissimus dorsi aponeurosis was then approximated with a running suture of plain No. 00 catgut and silk to the skin.

Postoperatively the movements of the subject were unrestricted as after the previous operation, but on the second postoperative day there was an elevation of temperature to 101°F. On examination at this time the wound appeared perfectly normal and it was left alone, the subject being admitted to the hospital for forty-eight hours. Thereafter he again continued his activities, unrestricted as before.

Wolbach, of the Harvard Medical School, showed lack of intercellular substance and capillary formation (Fig. 8), as had been found by Wolbach[3] in the wounds of scorbutic guinea pigs. This finding was in marked contrast to the section from the wound biopsy at the end of three months (Fig. 6).

Immediately after the biopsy the subject began daily to receive 1000 mg. of ascorbic acid intravenously, continuing as before on the same vitamin C-free diet (see below). After forty-eight hours the activities were again unrestricted, the drain being removed at this time. On the tenth postoperative day, another biopsy specimen was taken from this wound. There was good healing, the sections showing ample intercellular substance and capillary formation, as seen in Figures 9 and 10.

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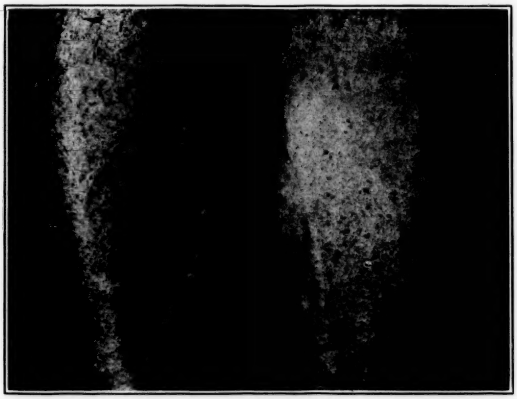

FIGURE 4. *Anterior View of the Lower Legs after Six Months of Vitamin C-Free Diet.*
Note the petechiae.

Teeth and Gums

During the first five months of the diet no changes were grossly apparent in the teeth or gums. A competent dentist pronounced the gums to be normal in appearance at the end of this time.

At the end of six months, when clinical scurvy, as manifested by the perifollicular hemorrhages over the legs, had been present for three weeks, examination of the gums and the teeth was made by Drs. A. P. Young and P. E. Boyle, of the Harvard Dental School. They found that the gums were slightly more boggy on pressure than usual, but no other gross changes could be seen. A biopsy specimen of the gingiva at this time was absolutely normal. Of interest is the fact that although the gross findings were negative, x-ray films of the teeth taken at this time showed occasional interruptions of the lamina dura.

Anemia

During the period of vitamin C deficiency there were four episodes of acute blood loss by venesection (Fig. 1). There was, moreover, mild, chronic loss of blood as a result of various blood determinations. In spite of this loss, which over the entire period of vitamin C deficiency amounted to slightly over 6000 cc., no anemia developed.† The hemoglobin showed a slight fall during the third month of the diet, but rose to normal after the intake of 0.5 gm. of ferrous sulfate daily (Fig. 1). During the week of intravenous vitamin C therapy the hemoglobin dropped sharply to 79 per cent as a result of a blood loss of about 120 cc. daily for plasma and white-cell-platelet determinations over a five-day period. This level was maintained for another week, in spite of cessation of blood loss and although there was a good reticulocyte response. With a normal diet, which included large amounts of orange juice daily, the hemoglobin thereafter rose rapidly, reaching 101 per cent after another ten days.

Leukopenia

At the onset of the experiment the white-cell count averaged around 5000, and no appreciable variation from this figure occurred until after one hundred and thirty-two days of the diet (Fig. 1). At this time the count fell to 3500, the differential count being normal. Except for slight rises following an episode of acute blood loss and after the last experimental wound, the white-cell count fluctuated between 3200 and 5000 during the rest of the experiment, remaining for the most part at the lower level. Following the administration of vitamin C there was a rise in the white-cell count to 5000 and later to 9000.

Infection

There was almost complete freedom from respiratory infection throughout the experimental period, covering the months of October to May. Only two very transient and mild attacks of coryza were noted, each lasting but a few days. In previous winters it has been not uncommon for the subject to suffer from frequent, severe upper-respiratory infections. Throughout the period of deficiency

†Hemoglobin determinations and other blood studies were done through the courtesy of Dr. E. L. Lozner, of the Thorndike Memorial Laboratory, Boston City Hospital.

there developed an occasional furuncle over the back of the neck, but each cleared up in normal time.

Blood-complement determinations* were done at the end of the third, fourth, fifth and sixth months of the diet, the last after clinical scurvy had been apparent for three weeks (Fig. 1). Each determination showed a perfectly normal titer as compared with a control.

Weight Loss

There was a gradual and continual weight loss for the first five and a half months of the experimental period, reaching a maximum of 27 pounds at the end of this time. This drop in weight can be criticized as adding an additional unknown factor to the experiment. We believe it difficult, however, for anyone to remain on a diet absolutely free of vitamin C over a long period without losing weight, since in order to avoid traces of the vitamin the diet must be restricted essentially to eggs, cheese, bread, butter and sucrose.

Fatigue

From the beginning of the third month of the diet there developed a feeling of fatigue which became progressively more marked. Measurement of this weakness was at first attempted by an ergograph. The number of contractions at the rate of one per second, made by the right hand against a standard resistance, showed only a slight drop during the period of vitamin C deficiency, falling from 59 at the outset to 42 at the end of the experiment. A week after institution of the ascorbic acid therapy, while the subject was still on the diet, the number of contractions increased slightly to 49, a rise which can hardly be considered significant.

At the end of the six months a fatigue test was carried out of the Fatigue Laboratory of Harvard University (Table 1). In order to determine the extent to which the capacity for work was reduced and to learn something about the mechanisms involved, the subject performed two grades of work on a motor-driven treadmill (walking and running). After ten days, during which the subject received vitamin C intravenously but remained on the deficient diet, the experiment was repeated. A control test was made seven weeks after the normal diet had been resumed. The data of Robinson[23] covering the same age group were used for comparison.

During a period of moderate work, — a walk for four and a half minutes on a grade of 8.6 per cent at a rate of 3.5 miles per hour, — both before and ten days after the beginning of vitamin C therapy, the subject's heart rate was nearly maximal, being about 40 beats per minute higher than on any of the men studied by Robinson. In the control test seven weeks later the heart rate after the same work was within normal limits. Throughout this moderate work the oxygen consumption was within normal limits in each experiment.

During a harder grade of work, — a run at a rate of 7 miles an hour to exhaustion, — the subject's performances while in the scorbutic state and directly after the vitamin C therapy showed considerable differences. In the state of complete vitamin C deficiency he was able to run for only 16 seconds, whereas following ascorbic acid therapy he ran for 66 seconds, in spite of the fact that at this second experiment the hemoglobin was 13 per cent lower and the oxygen capacity was 7.6 millimol. per liter as compared with 8.0 millimol. in the first test. In the control experiment after the normal diet had been resumed the subject ran for 84 seconds. This performance was still inferior to the 270-second average of other men of this age. Both before and after vitamin C therapy the maximal heart rates were about the same, reaching 190 beats per minute; and in both experiments during this maximal work the minute-oxygen consumption per kilogram of body weight was but three fourths the average found by Robinson. These were normal in the control experiment performed seven weeks later. This indicates an incapacity for aerobic work unrelated to vitamin C deficiency,

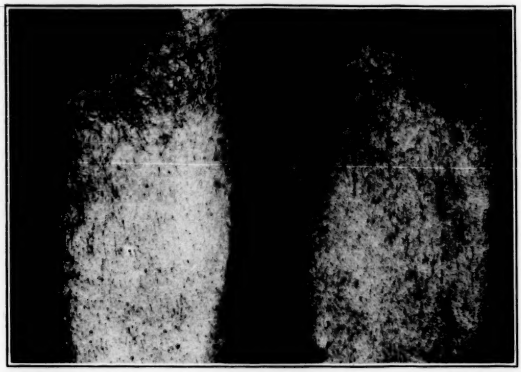

FIGURE 5. *Anterior View of the Lower Legs after a Week of Intravenous Vitamin C Therapy.*
Note the fading of the petechiae as compared with those in Figure 4.

*Blood-complement determinations were done through the courtesy of Dr. C. P. Emerson, of the Thorndike Memorial Laboratory, Boston City Hospital.

but does not diminish the significance of the better performance following vitamin C therapy. Despite his inability to reach a normal level of oxygen consumption while on the diet, the subject's capacity for anaerobic work, as measured by a hand ergograph, was undiminished, even while in the scorbutic state (Table 1).

The subject accumulated a lactate concentration of 82 mg. per 100 cc. before and 104 mg. after the administration of vitamin C. The oxygen debts were 3.29 and 4.97 liters, respectively. These higher figures after the vitamin C therapy were associated with the increased performance in the run. This may have been the result in part of improved skill, but it should be pointed out that the capacity for supplying oxygen was somewhat lowered in the second test.

TABLE 1. *Fatigue Tests.*

DATA	APRIL 26 (SCORBUTIC STATE)	MAY 6 (AFTER VITAMIN C THERAPY)	JUNE 26 (CONTROL)	NORMAL RANGE
Duration of work (min.)				
Moderate work	4.5	4.5	4.5	15
Maximal work	0.27	1.1	1.4	3–5
Ergograph (lb.)	52.0	49.0		40–70
Oxygen consumption (cc./kg./min.)				
Moderate work	29.9	27.7	27.3	25–30
Maximal work	37.8	36.7	40.3	40–50
Oxygen debt (liters)	3.29	4.97	5.55	
Heart rate (beats/min.)				
Moderate work	182	178	140	120–140
Maximal work	180	191	180	180–195
Recovery (1 min.)	161	180	140	140–160
Recovery (10 min.)	105	108	112	80–120
Recovery				
Oxygen consumption (liters)				
0–3 min.	2.58	2.87	3.48	
3–15 min.	5.02	5.54	5.52	
Blood lactate (mg./100 cc.)				
5 min.	82.0	104.4	104.0	
10 min.	65.1	105.5	93.3	
15 min.	51.6	87.6	75.6	
30 min.	28.1	51.6	35.6	
45 min.	22.4	22.4	32.2	
60 min.	24.7	15.7		
Blood sugar (mg./100 cc.)				
5 min.	127	122	125	
10 min.	94	115	114	
15 min.	100	113	120	
30 min.	100	104	110	
45 min.	109	99	118	
60 min.	106	106		
Insulin-tolerance curve (sugar in mg./100 cc.)				
2 min.	88	100		
10 min.	83	90		
15 min.	76	80		
20 min.	74	72		
25 min.	66	65		
35 min.	67	70		
45 min.	69	83		
60 min.	74	100		

The performance of the subject while in the scorbutic state placed him in the same category as the Group X of Robinson, consisting of men in the eighth decade of life, for whom the five-minute walk was maximal work. The heart rate during recovery was higher than that observed by Robinson. Following treatment with ascorbic acid the rate fell more rapidly during recovery, despite a slightly higher initial value, a higher blood lactate concentration and a greater oxygen debt.

Of considerable interest are the blood lactate levels following the fatigue test performed when the subject was in a scorbutic state. There was a normal rate of disappearance of the blood lactate for the first fifteen minutes of the recovery period. During the following half hour the rate of disappearance was much decreased, being about half the normal rate. After the vitamin C therapy the rate of disappearance of the blood lactate was normal throughout the recovery periods of the tests made while the subject was still on the diet and also following the control run seven weeks later.

Studies made on samples of arterial blood, drawn when the subject was in the basal state, before and after treatment, showed no abnormalities except for a slight anemia (Table 2).

TABLE 2. *Arterial Blood Studies Before and After Vitamin C Therapy with the Subject in a Basal State.*

DATA	APRIL 26 (SCORBUTIC STATE)	MAY 6 (AFTER VITAMIN C THERAPY)	NORMAL RANGE
Carbon dioxide content (millimol./liter)	21.8	21.5	20.0 – 23.0
Hemoglobin oxygen concentration (millimol./liter)		7.10	8.0 – 9.5
Hemoglobin oxygen capacity (millimol./liter)	8.04	7.60	8.52– 9.44
Hemoglobin oxygen saturation (per cent)		93.5	93.0 – 97.0
Serum carbonic acid (milliequiv./liter)	2.92	3.10	2.4 – 3.2
Serum bicarbonate (milliequiv./liter)	25.3	23.8	24.0 – 27.0
Arterial carbon dioxide pressure (mm.Hg)	42.0	44.4	35.0 – 45.0
Plasma pH	7.40	7.34	7.35– 7.45
Lactate (milliequiv./liter)	1.0		1.0 – 1.5
Sugar (mg./100 cc.)	111.0		90.0 –110.0
Plasma chloride (milliequiv./liter)	107.1	106.4	103.0 –107.0
Plasma protein (gm./liter)	62.0	65.2	63.0 – 68.0
Plasma inorganic phosphorus (milliequiv./liter)	2.4	1.7	1.6 – 3.2

Basal Metabolic Rate

Basal metabolic rates were frequently determined by the Benedict-Roth method, beginning prior to the dietary period and continuing during the administration of parenteral vitamin C, while the subject remained on the diet (Fig. 1). During the dietary period the metabolic rate fell as low as —22 per cent, but after the administration of vitamin C was started, while the subject was still on the diet, values as low as —18 per cent were obtained. At the Harvard Fatigue Laboratory, where the metabolic rate was determined by the open-circuit gasometer method, there was an increase from —6 to —3 per cent after the institution of vitamin C therapy. It is doubtful, therefore, whether the fall in basal metabolic rate could in any way be attributed to vitamin C deficiency. It was probably due to weight loss or inanition or both. Basal metabolic rates were done daily after the parenteral ascorbic acid was started, both before its administration and one and a half to two hours thereafter. It is interesting that during the first four days the basal metabolic rate uniformly fell after the administration of 1000 mg. of ascorbic acid intravenously (Table 3). During this time the subject was becoming saturated with the vitamin (see below). Following this period of saturation, the basal metabolic rate two hours after the administration of ascorbic acid was consistently higher than it was before its injection.

Capillary Fragility

During the entire experiment the capillary fragility test, as described by Göthlin,[24, 25] remained absolutely negative (Fig. 1). At the end of five months, when the petechiae were beginning to appear over the legs, a pressure of 100 mm. of mercury was applied to the arm for ten minutes by means of a blood-pressure cuff. This brought out twenty-two petechiae in a measured area 6 cm. in diameter. Among 8 controls, 7 showed more petechiae at the end of ten minutes than did the subject. Dr. C. J. Farmer, at Northwestern University, performed a negative-pressure (Dalldorf[26]) test on the arm of the subject after five months and two weeks of dieting. This also was perfectly normal, 450 mm. (mercury) of negative pressure being required to produce any petechiae.

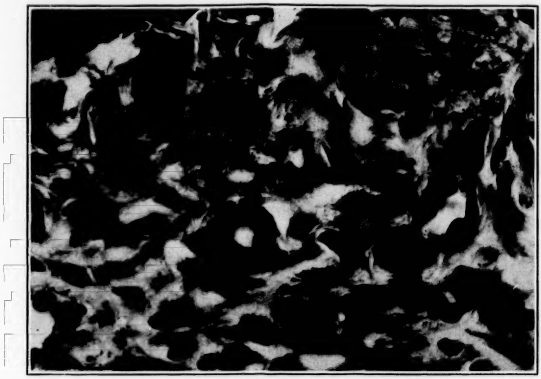

FIGURE 6. *Biopsy Specimen Removed after Three Months of Vitamin C-Free Diet: Eosin and methylene blue stain (× 650).*

Note the numerous capillaries and the abundance of intercellular substance in the granulation tissue.

TABLE 3. *Effect of Intravenous Ascorbic Acid (1000 mg.) on the Basal Metabolic Rate of the Scorbutic Subject.*

DATE	BASAL METABOLIC RATE BEFORE THE INJECTION OF VITAMIN C %	BASAL METABOLIC RATE 1½ HR. AFTER THE INJECTION OF VITAMIN C %
April 28	0.0	− 3.0
April 29	−15.4	−16.4
April 30	− 7.5	−11.2
May 1	0.0	−18.7
May 2	−16.7	− 9.0
May 3	− 3.3	− 3.3
May 4	−12.3	− 8.3

Blood Pressure

The blood pressure remained at a constant level of 120 systolic, 70 diastolic, until immediately following the fourth episode of blood loss on the one hundred and fifty-fifth day of the diet, when it fell to 90/60. During the next week the systolic pressure rose to 98, but it never exceeded this level until the ascorbic acid was started, when it promptly rose.

Muscle Phosphorus and Phosphagen

At the time of biopsy of the second experimental wound a portion of sacrospinalis muscle was removed and subsequently analyzed for total soluble phosphorus and for phosphagen phosphorus content.* The total phosphorus content was low, being only 111.5 mg. per 100 gm. of muscle. The phosphagen phosphorus content was high, being 50.4 mg. per 100 gm. of muscle, or 45 per cent of the total phosphorus content. In normal muscle the phosphagen is only about 35 per cent of the total soluble phosphorus.

After a ten-day period, during which the subject remained on the same vitamin C-free diet but daily received 1000 mg. of ascorbic acid intravenously, another piece of muscle was analyzed, this time from the thigh. The total soluble phosphorus was considerably increased, being 145.9 mg. per 100 gm., while the phosphagen phosphorus was only 45.6 mg. per 100 gm., or 31 per cent of the total muscle phosphorus.

Miscellaneous

Two insulin-tolerance tests were done (Table 1).† Each was obtained following the intravenous injection of 3.1 units of insulin. The tests were made under identical conditions, and while the subject was in the basal state. It is apparent that vitamin C had no influence on insulin tolerance. Glucose-tolerance tests were also normal.

A gastric analysis done after five months of the diet showed only 1 unit of free acid and only 3 units of total acid, and after histamine 22 units of free acid and 27 units of total acid. After eleven days of intravenous administration of ascorbic acid, while the subject was still on the diet, analysis of the gastric contents again showed only 1 unit of free acid and 3 units of total acid, but this time, after the administration of histamine, there were 33 units of free and 42 units of total acid.

*Muscle-phosphorus and muscle-phosphagen-phosphorus determinations were done through the courtesy of Dr. Steven Horvath, of the Harvard Fatigue Laboratory.

†Insulin-tolerance tests were done through the courtesy of Dr. John W. Thompson, of the Harvard Fatigue Laboratory.

Other determinations, which included serum proteins, lipids, sedimentation rates, hematocrits, bleeding and clotting times, examination of stools and urines for blood (with complete analysis of the latter), chest x-ray films and electrocardiograms, were within normal limits (Fig. 1). There was a slight fall of the blood-sodium level from 142 to 136 milliequiv. per liter just before the ascorbic acid was begun. Following six days of ascorbic acid therapy the blood sodium regained the normal level.

An electroencephalogram made between the fourth and fifth months of the diet was negative.*

Saturation of Vitamin C

Following the first biopsy of the second experimental wound, saturation with vitamin C was begun, the same vitamin C-free diet being continued. For this purpose 1000-mg. doses of ascorbic acid were given daily after the manner of Wright, Lilienfeld and MacLenathen.[27] It was believed that the intravenous route was the best method of saturation, since oral doses may introduce unknown and perhaps variable absorption factors[28–30] as well as a time factor in the ensuing saturation curves. After preliminary plasma and white-cell-platelet determinations, the vitamin was injected, following which hourly plasma and urine determinations were done. The plasma and urine determinations are represented in Figure 11.

Early in the experiment it had been found that even with a plasma of zero and no intake of the vitamin, the titration method of Harris[11] gave considerable values in the urine, undoubtedly owing to the presence of reducing substances other than vitamin C.[31] For this reason the recently described method of Evelyn, Malloy and Rosen[12] was used.

It can be seen on examination of Figures 11 and 12 that on the first day the plasma C content fell very rapidly during the first three hours after injection of the vitamin, reaching zero at the end of five hours. On each succeeding day the initial plasma and also the white-cell-platelet levels were higher, the latter being 3, 16 and 28 mg. per 100 cc. respectively on the first three days of the saturation regime. This almost normal white-cell-platelet value on the third day, together with the very gradual drop in the plasma level of the vitamin on that day, may be taken as indication that saturation of the *blood* occurred somewhere between the third and fourth days.

Examination of the urinary output of the vitamin immediately reveals that the amount, as determined by the Evelyn–Malloy[12] method, is much smaller than has been obtained by the Harris titration method, if the subject may be considered saturated after the fourth day. In determining the values in the urine, great care was taken in our laboratory to avoid any ceiling in the method by multiple dilutions of the urine samples.

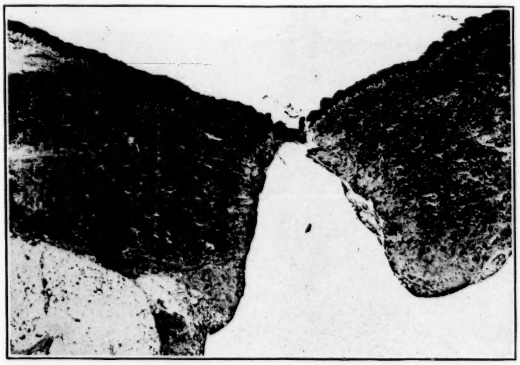

FIGURE 7. *Biopsy Specimen Removed after Six Months of Vitamin C-Free Diet: Eosin and methylene blue stain (× 15).*

This section shows complete lack of healing. The large space was occupied by an unorganized blood clot.

It becomes evident, on examination of Figure 11, that there is an apparent renal threshold, as described by Faulkner and Taylor,[32] using the Harris titration. According to our findings, however, this threshold does not occur at a plasma value of 1.4 mg. per 100 cc., as described by them and others, but rather with a plasma value of about 0.85 mg. in the normal adult, as shown by the April 30 figures. Moreover, the plasma saturation and urinary excretion curves suggest that in the totally vitamin C-deficient state this renal threshold may be lower, and that as saturation with vitamin C takes place it rises to normal (April 27 to 30 figures). On the other hand, the appearance of ascorbic acid in the urine coincidental with low plasma levels (in the first three curves) may be due to a lag phenomenon.

Examining the curves again, it may be noted that during the process of saturation with vitamin C the output of the vitamin in the urine was on two occasions greater during the second hour than during the first hour (April 30 and May 2). On these two days the volume of urine excreted was considerably greater during the second hour than during the first hour. On the other days during the saturation period the volume was greater in the first than in the second hour, and it will be noted that the excretion of the vitamin was also always greatest during

*Electroencephalography was performed through the courtesy of Dr. F. A. Gibbs, of the Boston City Hospital.

the first hour. This would suggest that while the organism is in a vitamin C-deficient state the output of ascorbic acid may depend not only on its plasma level and on the renal threshold but also on the amount of urine excreted. Of interest in this respect is the finding of Sendroy and Miller[33] that renal function is a factor in the excretion of ascorbic acid, and that of Wright and MacLenathen [34] that vitamin C may be excreted slowly in cases of kidney damage. Following saturation of the subject, however, the excretion of vitamin C was always greatest during the first hour after the injection, no matter how the urinary output was made to vary.

Effect of Vitamin C Therapy

Within twenty-four hours after the administration of the vitamin a subjective improvement was noted, there being a marked alleviation of weakness and languor. This improvement seemed to progress during the next four or five days. It is possible, of course, that considerable or even all the effect was due to suggestion.

The skin changes were remarkable. At the end of six days the petechiae had faded considerably, and the skin had returned from a rough to a smooth state, although hyperkeratotic papules were still present. Between twelve and fourteen days after the institution of the vitamin C therapy the petechiae had entirely disappeared, but traces of the papules remained over the buttocks for three weeks.

Although the hemoglobin fell following the commencement of vitamin C therapy, it is of interest that the blood pressure, which had been somewhat below the subject's normal since the last episode of acute blood loss, almost immediately began to rise after the vitamin C had been given.

On the third day after the vitamin was begun a slight blurring of vision was noticed when the eyes were focused on distant objects. This cleared up in twenty-four hours, and may have been due to diffusion of ascorbic acid into the lens.

Except for the increased ability to do aerobic work, as measured by the fatigue test, and, of course, the wound healing, there were no noteworthy changes during the vitamin C therapy while the subject remained on the diet. There was no gain in weight during this time.

Comment

Wound Healing

Since the emphasis by Wolbach and Howe[2] that the fundamental lesion of scurvy is a deficiency of intercellular substance and capillary formation, there has been increased interest in the surgical significance of the vitamin. The experimental work of Lanman and Ingalls[4] and of Taffel and Harvey,[35] showing that the wounds of scorbutic guinea pigs healed slowly and with poor tensile strength, received support from the clinical work of certain investigators,[36–39] notably Wolfer, and Archer and Graham. The clinical evidence for the necessity of the vitamin for wound healing lay somewhat open to question, however, since the cases reported were, of necessity, poorly controlled with respect to other variable factors important in wound healing, notably other avitaminoses, infection, surgical technic and so forth. Although it is to be remembered that only one case is considered here, all such variables were excluded, and the lack of wound healing must be attributed to ascorbic acid deficiency alone. The mere fact that the biopsy sections showed striking resemblance to those from the wounds of scorbutic guinea pigs would appear as conclusive evidence that the lack of healing was due not to infection, in-

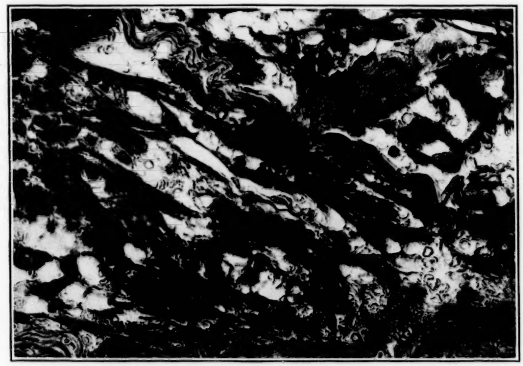

FIGURE 8. *Biopsy Specimen Removed after Six Months of Vitamin C-Free Diet: Eosin and methylene blue stain (× 350).*

Note the newly formed fibroblasts having no intercellular substance between them. Old collagen may be seen at the bottom and extending down and to the right from the upper left-hand corner.

creased tension or other such factors but to vitamin C deficiency.

Significance of Plasma-Vitamin C Levels

It should be kept in mind that normal wound healing occurred after three months of vitamin C deficiency, when the plasma ascorbic acid had been zero for as long as forty-four days.[15] This, together with the other negative findings at that time, suggests that the plasma ascorbic acid is a poor index of the vitamin C status of the patient.

Lack of controlled cases may possibly be responsible for the general belief that the plasma levels of the vitamin are a fair index of deficiency and that levels below 0.5 mg. per 100 cc. are dangerously low.[39, 40] As pointed out by Butler and Cushman,[10] it would seem that the white-cell-platelet level of the vitamin in the centrifuged blood is a much more accurate measure of deficiency. In this case the level reached zero just ten days before the hyperkeratotic papules appeared, and thirty days before the appearance of the petechiae, at which time the plasma had been zero for one hundred and twenty days.

Why did so much time elapse before clinical scurvy appeared in this subject? The answer to this question must lie in the fact that there were no complicating factors such as growth, infection or multiple avitaminosis. That Stark[14] showed signs of scurvy within ten weeks on a diet almost totally deficient in all the vitamins suggests that multiple avitaminosis may bring on clinical vitamin C deficiency more rapidly. And it is to be remembered, of course, that clinical vitamin C deficiency is practically always associated with some deficiency of vitamin B, and perhaps also of the other vitamins. There is a known increased disappearance of vitamin C from both plasma and white cells in cases with infection,[41–48] and when growth or hyperthyroidism is a factor.[49, 50] It is possible, moreover, that extreme muscular exertion may deplete the body of the vitamin more rapidly, and that scurvy would have appeared in the experimental subject much sooner had he been constantly subjected to extreme muscular fatigue.

FIGURE 9. *Biopsy Specimen Removed after Ten Days of Intravenous Vitamin C Therapy: Eosin and methylene blue stain (× 15).*

This section shows complete healing of both the original wound and that of the biopsy ten days later.

Human Requirement

Much has been written on the vitamin C requirement of human adults, and many methods[17, 18, 31, 51–56] have been evolved and employed for its estimation. The majority are necessarily based on the assumption that saturation is the optimal state for the individual, a postulate having little evidence for its support. Estimations of the daily requirement have varied between 20 and 100 mg. per 100 cc., the majority of workers setting 30 mg. as the daily minimum.[54]

It is unfortunate that in this experiment the point at which the subject became saturated cannot be accurately determined. Although the blood level of the vitamin had returned to normal by

the fourth day of the saturation period, the urinary output was not maximal by the sixth day. Taking into consideration the total amount lost in the urine (about 1 gm.) 4 to 6 gm. may be considered as roughly the maximal amount of ascorbic acid necessary to resaturate this individual. Since the first signs of scurvy appeared after one hundred and thirty-two days of total vitamin C deficiency, the maximal daily utilization of the vitamin must have been between 30 and 45 mg. It is possible that the true requirement lies somewhat below this figure. On the other hand, this estimate would of course be elevated if infection, multiple avitaminoses, hyperthyroidism and possibly increased exertion had been factors in the experiment.

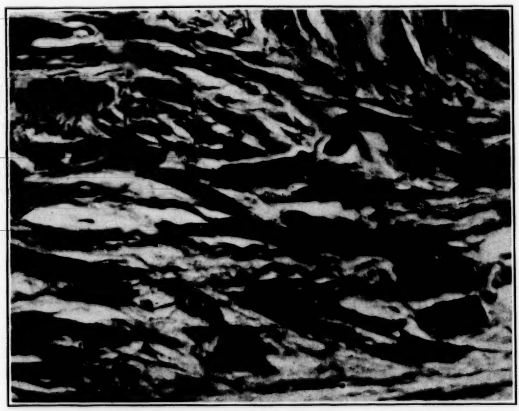

FIGURE 10. *Biopsy Specimen Removed after Ten Days of Intravenous Vitamin C Therapy: Eosin and methylene blue stain (× 600).*
Note the abundant, newly formed fibroblasts, with collagen between them.

Teeth and Gums

Grossly the teeth and gums showed no marked changes during the entire dietary period, although very slight bogginess was found one week before the institution of vitamin C therapy. On brushing the teeth there was no trace of bleeding at any time. Immediately after the fatigue test, while in the scorbutic state, however, the subject did show for the first and only time a small hemorrhage at one gingival margin, a finding which suggests that had he been exposed to such fatigue throughout the experiment, signs of scurvy might have appeared much earlier. The lack of changes in the gums and teeth during the entire period raises the question, however, as to whether those commonly described[57] as typical of scurvy may not be at least in part due to pre-existing or superimposed gingivitis or dental caries or both. Supporting this hypothesis is the fact that in edentulous scorbutic patients no gingival changes are commonly seen. Of interest are the x-ray films of the teeth taken during the scorbutic state, particularly since they are consistent with the alveolar lesions found by Boyle in scobutic guinea pigs.[58–60] In these films slight but definite interruptions of the lamina dura can be made out, which presumably result from atrophy of alveolar bone and its replacement with collagen-free fibrous tissue. Slight but definitely noticeable changes toward the normal could be discerned in the roentgenograms taken five weeks after the subject had resumed a normal diet. It is possible that x-ray films showing such interruptions of the lamina dura may be one of the best criteria for the diagnosis of incipient scurvy.

Anemia

The fact that no appreciable anemia occurred in the subject until the administration of ascorbic acid was begun, in spite of a blood loss of over 6000 cc. during the six-month period, is not in accord with the conclusions of Mettier, Minot and Townsend[61] and of Parsons and Hawksley[62]—which have already been challenged by several workers, notably Cooley[63] and Gingold[64]—to the

effect that vitamin C deficiency per se may cause diminished hematopoiesis.

Resistance and Infection

There is at present a widespread belief that vitamin C deficiency is an important cause of lowered resistance to infection. This is based in part on the well-known fact that there is much more rapid disappearance of the vitamin from

Leukopenia

During the dietary period there was a slight fall in the white-cell count, but since the normal count for the subject was apparently only 5000, this cannot be considered as significant. The rise to 9000 occurring after the beginning of vitamin C therapy is consistent with the findings of other workers,[73] who have noted moderate leukocytosis

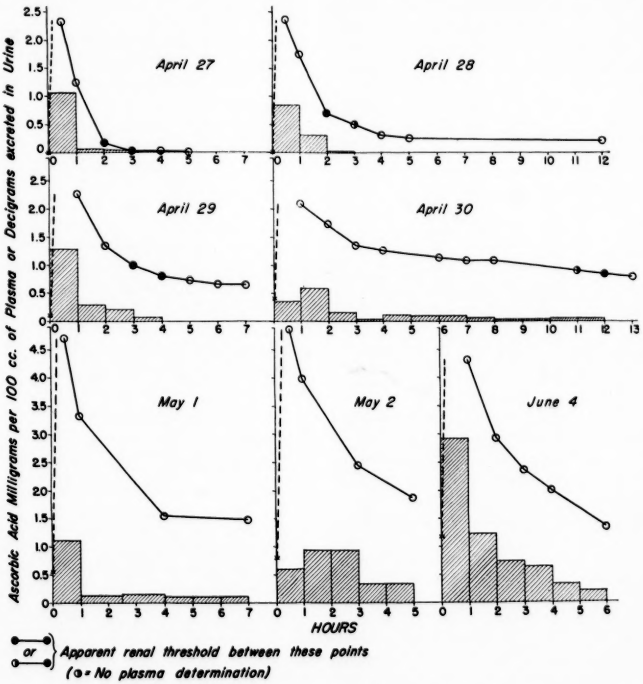

FIGURE 11. *Plasma and Urine Vitamin C Levels Following Saturation with Ascorbic Acid.*

both plasma and tissues in cases of infection, and in part on results in experimental animals.[65–69] Moreover, Ecker[70, 71] and others[72] have recently reported lowered titers of blood complement in scurvy. Although the literature supporting the value of vitamin C in sepsis is extensive, the complete lack of infection in this experimental subject over the period of deficiency raises doubt as to whether vitamin C per se is a marked factor in lowering the resistance of an adult. Moreover, blood-complement titers showed no fall whatsoever even after the appearance of frank scurvy. following the intravenous administrations of ascorbic acid in cases of leukopenia.

Fatigue

The belief that scurvy is characterized by languor and incapacity for work is well borne out by this experiment. Subjectively, weakness was first noticed at about the end of the third month, becoming progressive as time went on. Although no marked change could be found in the muscular activity of the forearm as measured by an ergograph, both for a single contraction and for

contractions each second to exhaustion, the results when the subject ran on a treadmill were striking. Although a considerable part of his inability to run over 16 seconds must be attributed to factors other than vitamin C deficiency, he was able to run 66 seconds following the parenteral administration of ascorbic acid while on the same diet, even though the hemoglobin was 13 per cent lower. Of interest, also, is the fact that the heart rate fell more rapidly during the recovery period following the administration of the vitamin. Moreover, it will be noted that the blood lactate curve was definitely abnormal in the scorbutic state. No hint as to the underlying physiologic mechanisms responsible for these differences before and after therapy could be gleaned from the laboratory determinations made coincidentally with these fatigue tests.

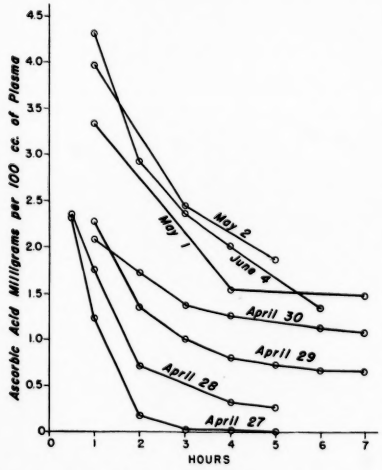

FIGURE 12. *Plasma Vitamin C Saturation Curves.*

Capillary Fragility

It should not be concluded that capillary fragility is not part of the underlying pathology of scurvy merely because the Göthlin and Dalldorf tests were negative throughout the experiment. The appearance of the petechiae in the lower extremities after a long period of standing suggests that hydrostatic pressure and capillary fragility were factors in their etiology. The experimental results suggest, however, that neither the Göthlin nor the Dalldorf test is a good measure of capillary fragility in early scurvy. Certainly this would seem to throw serious doubt on the contention that such tests are a good index of subclinical vitamin C deficiency,[74] in spite of the fact that frequently in cases of scurvy such tests are positive, and that in many such cases vitamin C therapy rapidly clears up all signs of such abnormal fragility. Lack of correlation between capillary fragility and vitamin C deficiency is also being found by other workers,[75] and notably Farmer.[76]

Blood Pressure

Of possible significance was the fall in blood pressure which occurred and persisted after the last episode of acute blood loss (one hundred and fifty-fifth day), since it returned to normal after the administration of vitamin C, in spite of continuation of the vitamin C-free diet and blood loss. Pertinent in this respect are the facts that in animals relatively large amounts of vitamin C are stored in the adrenal glands, and that scorbutic guinea pigs have diminished adrenocortical hormone[77] and at autopsy show atrophy of the adrenal cortex.[78] Toward the end of the experiment, almost coincidentally with the fall in blood pressure, the blood sodium fell to 136 milliequiv. per liter, rising to 142 milliequiv. directly after vitamin C therapy. Whatever the cause of this lowered systolic pressure, it was not due to diminished blood volume, for this was normal at the end of the six-month period, as measured by the Gibson method.

Glucose and Insulin Tolerance

There are at present many conflicting views as to the effect, if any, of vitamin C on carbohydrate metabolism. It has been reported that there is a lowered glucose tolerance in scorbutic guinea pigs[79] and that the administration of vitamin C results in increased sensitivity to insulin both in normal subjects and in diabetic patients.[80–84] In contrast to these findings are the entirely negative results of other workers[85–87] who have been unable to show any relation between vitamin C and carbohydrate metabolism. In agreement with the latter conclusions are the insulin-tolerance and glucose-tolerance curves of the experimental subject, which were within normal limits while he was in the scorbutic state.

Basal Metabolic Rate

Because vitamin C has relatively strong reducing properties, there is a widespread belief that it serves primarily as a "hydrogen transport agent."[88] Here again the experimental findings are in conflict, some investigators[89, 90] reporting a decrease in metabolic rate in scorbutic guinea pigs, others[91] an increase.

Since the basal metabolic rate of the experimental subject dropped to almost as low a level following the beginning of vitamin C therapy as during the period of deficiency, the variations during this period cannot be considered significant. These findings are in accord with the results of other workers.[92] Of interest, however, is the fact that during the saturation of the subject with vitamin C, the basal metabolic rate fell slightly directly after each injection of the vitamin, whereas after saturation had been completed no such fall occurred. Although this fall was constant during the saturation period it was generally very slight, and its significance may therefore be open to question. A significant drop in metabolic rate following the administration of parenteral ascorbic acid to a scorbutic individual would, of course, suggest that by the introduction of the vitamin the individual's efficiency for utilization of oxygen was increased.

Metabolism of Vitamin C

What part does vitamin C play in the physiology of the human organism other than as a prerequisite for the formation of intercellular substance? This question must at present remain unanswered. The abnormal blood lactate curves during the recovery period of the scorbutic subject after the fatigue test, the variations of the metabolic rate and the abnormal phosphorus and phosphogen contents of the striated muscle, all may serve as leads for future investigations into the metabolism of vitamin C.

Summary and Conclusions

A normal active adult placed himself on a vitamin C-free diet supplemented by the other known vitamins for a period of six months. The findings in this state of pure vitamin C deficiency, that is, in the absence of factors such as multiple avitaminoses, infection, growth or other stress, were as follows:

One hundred and thirty-two days of a diet totally deficient in vitamin C were required for the first abnormal clinical signs — hyperkeratotic papules — to appear; 161 days were necessary for the appearance of the perifollicular hemorrhages of scurvy.

The plasma-ascorbic acid level was zero for thirteen weeks before the first evidence of clinical scurvy was manifest. It is not necessarily, therefore, a good index of the vitamin C status of the individual.

The vitamin level in the white-cell-platelet layer of the centrifuged blood was a good index of the vitamin C status of the subject. This level fell to zero shortly before the appearance of clinical scurvy.

Adequate wound healing occurred after the plasma-ascorbic acid had been zero for forty-four days and when the white-cell-platelet ascorbic acid level was 4 mg. per 100 cc.

With total vitamin C deficiency, failure of wound healing occurred. The tissues under these circumstances showed microscopically a lack of intercellular substance. Parenteral vitamin C alone brought about good healing, and considerable intercellular substance appeared within ten days.

Hyperkeratotic papules containing ingrown hairs appeared over the buttocks and posterior aspects of the legs as a result of vitamin C deficiency; indeed, they may be the first sign of such a deficiency.

There were no gross changes in the gums or teeth (with good pre-existing oral hygiene). Although the mouth was grossly negative, x-ray films of the teeth showed interruptions of the lamina dura in early acute scurvy. Such an x-ray picture may be one of the better diagnostic criteria in early scurvy.

Vitamin C deficiency did not produce anemia.

After prolonged vitamin C deficiency there was inability to perform aerobic work, although the capacity for anaerobic work was undiminished. After a period of aerobic work in the scorbutic state the rate of disappearance of the blood lactate was abnormally slow.

During a six-month period of total deficiency and after a month of clinical scurvy the blood-complement titer was still normal. Over this period there was no evidence of lowered resistance to infection.

The Göthlin, Dalldorf and Rümpel-Leeds tests were negative, even in the presence of frank scurvy. These tests must therefore be poor indices of subclinical scurvy, even though they may in some cases produce petechiae which are cleared up by ascorbic acid therapy.

With severe vitamin C deficiency there was a fall in the blood pressure.

There was a lowering of the total phosphorus content of striated muscle, with an increase in the phosphagen phosphorus.

All the signs and symptoms of scurvy rapidly disappeared following the intravenous injection of ascorbic acid.

When the state of deficiency was complete the plasma-ascorbic acid level fell to zero in five hours after injection of 1 gm. of the vitamin.

Although the blood became completely saturated (as measured by plasma saturation curves and white-cell-platelet levels) after 3 or 4 gm.

of ascorbic acid had been given intravenously, the tissues were not completely saturated at this time, since the urinary output of ascorbic acid was still well below maximal over a six-hour period.

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ALPHA AND BETA NEUTRAL KETOSTEROIDS (ANDROGENS)*

Preliminary Observations on Their Normal Urinary Excretion and the Clinical Usefulness of their Assay in Differential Diagnosis

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THIS paper reports preliminary data on the twenty-four-hour urinary excretion of alpha, beta and total neutral ketosteroids‖ by normal individuals of both sexes and of varying ages and by patients showing male sexual precocity or virilism.

The available evidence[1-7] indicates that the neutral ketosteroids (17-ketosteroids) arise from substances produced by the adrenal glands and male gonads. The total output is therefore considered to be a rough index of the combined activity of these two glands. The isolation of individual ketosteroids by Callow et al.,[2-5, 7, 8] Butler and Marrian,[10] Hirschmann[11] and Dorfman, Cook and Hamilton[12] affords evidence that whereas the alpha neutral ketosteroids probably arise from adrenal and gonadal secretions, the beta neutral ketosteroids are an excretion product only of the cells of the adrenal cortex.

Accepting this evidence as a working hypothesis, the rate of beta neutral ketosteroid excretion by the subjects mentioned above has been determined by a relatively simple but directly quantitative colorimetric method reported elsewhere.[13]¶ The data obtained not only augment the evidence favoring the adrenal cortex as the source of beta ketosteroids, but also provide specific diagnostic criteria for the differentiation of adrenocortical hyperplasia, Cushing's syndrome without adrenal tumor and adrenocortical carcinoma.

RESULTS

The data obtained on normal subjects (Table 1) show the following:

The average daily excretion of total neutral ketosteroids of children under seven years of age was very low (1.3 mg.). It increased with age, reaching an average of 4.0 mg. between seven and twelve years and 8.2 mg. between twelve and fifteen years. Adult men tended to excrete more ketosteroids (15.0 mg.) than did adult women (10.2 mg.). The level of total excretion of pregnant women (15.1 mg.) approximated that of adult men.

The average daily alpha neutral ketosteroid excretion paralleled the total output. The aver-

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‖The terms "alpha" and "beta" refer to the spatial position of the 3-hydroxyl group. The chemical separation of alpha and beta neutral ketosteroids as discussed here depends on the fact that beta ketosteroids (which include dehydroisoandrosterone and isoandrosterone) may be precipitated with digitonin, leaving the other, or alpha, ketosteroids (such as androsterone and etiocholane-3-[α]-ol-17-one) in solution. The difference in the ketosteroid content of solutions before and after precipitation, therefore, gives the beta ketosteroid content.

¶In any comparison of the data obtained by this method, due consideration should be given to the procedure employed for hydrolyzing and extracting the urines. The data reported here were obtained on individual twenty-four-hour specimens which were hydrolyzed by the commonly employed procedure of boiling for ten minutes with 150 cc. of hydrochloric acid per liter of urine, followed by immediate extraction of the hormones in a rapid, benzene[14] or carbon tetrachloride extractor.[15] Recent experiments in our laboratory indicate that this method of hydrolysis is not optimal. It results in some destruction of unconjugated hormone and some replacement of the beta hydroxyl group, on which the estimation of the beta fraction depends. Consequently, the results reported may include an underestimate of the total excretion and of the beta fraction and an overestimate of the alpha fraction. These errors will be considered in detail in a forthcoming paper.[32] They do not alter the significance of the data reported here.

age daily beta neutral ketosteroid excretion comprised 8 to 15 per cent of the average total output. The excretion of adult men (1.2 mg.) and that of normal adult women (1.1 mg.) were essentially the same, while that of pregnant women (1.9 mg.) was, considering the hydrolysis procedure, suggestively higher.

Table 2 gives data on the average daily excretion of neutral ketosteroids by 10 abnormal individuals. Of these, 8 presented definite abnormalities of the secondary sex characteristics, such as a precocious development of the penis to adult size or an abnormally large clitoris; the remaining 2 patients suffered from Cushing's syndrome. Brief summaries of the case reports follow:

TABLE 1. *Average Excretion of Alpha, Beta and Total Neutral Ketosteroids by Normal Subjects.**

TYPE OF SUBJECT	NO. OF CASES	AVERAGE ALPHA NEUTRAL KETOSTEROIDS	BETA NEUTRAL KETOSTEROIDS		TOTAL NEUTRAL KETOSTEROIDS	
			AVERAGE	RANGE	AVERAGE	RANGE
		mg. per 24 hr.	*mg. per 24 hr.*	*mg. per 24 hr.*	*mg. per 24 hr.*	*mg. per 24 hr.*
Children						
4 to 7 yr. ...	5	1.2	0.1	0.0–0.2	1.3	0.8– 2.6
7 to 12 yr. ..	10	3.7	0.3	0.0–0.5	4.0	1.8– 5.0
12 to 15 yr. .	7	7.5	0.7	0.0–2.7	8.2	5.0–11.3
Women, 15+ yr.	9	9.1	1.1	0.0–2.5	10.2	6.5–17.4
Men, 15+ yr. ..	5	13.8	1.2	0.0–1.8	15.0	12.3–18.5
Women, 4 to 7 mo. pregnant.	4	13.2	1.9	0.0–4.0	15.1	10.8–20.4

*Forty-nine determinations were made on 40 subjects who were hospital staff members or patients presenting no obvious evidence of endocrine disorder.

TABLE 2. *Excretion of Alpha, Beta and Total Neutral Ketosteroids by Abnormal Patients.*

CASE NO.	ALPHA NEUTRAL KETOSTEROIDS	BETA NEUTRAL KETOSTEROIDS	TOTAL NEUTRAL KETOSTEROIDS
1. Preoperative*	13.0	4.0	17.0
Postoperative (2 yr.)†	17.5	4.5	22.0
2. Preoperative*	29.0	0.0	29.0
Postoperative (4 mo.)†	24.0	4.0	28.0
3	29.0	1.0	30.0
4	45.5	5.5	60.0
5	14.0	1.0	15.0
6	13.8	1.0	14.8
7	9.8	1.4	11.2
8	1.7	0.5	2.2
9	56.0	104.0	160.0
10	83.0	83.0	166.0

*Preoperative measurements.
†Measurements made 2 years postoperatively in Case 1 and 4 months postoperatively in Case 2.

CASE 1 (C. H. No. 142513: adrenogenital syndrome). The patient, an 8-year-old boy, was apparently normal until 4 years of age, when his penis began to enlarge and he started to grow rapidly in height. Shortly afterward pubic hair and acne appeared. The history was not otherwise remarkable. On physical examination the patient's general appearance was masculine. He was 61.5 inches in height and weighed 83.5 pounds. The skeletal age was advanced to that for the average 12-year-old boy. The musculature, although well developed, was not excessive. The voice was bass. There was marked acne of the face and thorax. Pubic hair was well developed, and the penis was of adult size. The testes, however, were of normal size for his age. No spermatozoa were observed in the urethral discharge obtained after prostatic massage. Visual-field and eyeground examinations revealed no abnormality. Ventriculoencephalogram showed slightly enlarged lateral and third ventricles. The fourth ventricle appeared to be normal. The blood pressure was 110/60. Intravenous pyelograms showed the left kidney to be rotated slightly away from the midline, a change interpreted as consistent with the presence of a tumor in the region of the left adrenal gland. Dr. Thomas H. Lanman explored both adrenal glands. The right appeared to be normal, the left to be enlarged. The latter was removed and examined by Dr. Sidney Farber. In his opinion there was hypertrophy and hyperplasia of the cortex without evidence of tumor. During the 1st postoperative year there was a temporary decrease in the acne, associated with a temporary fall in the neutral ketosteroid output to half the preoperative level. Two years later, however, there was no striking difference between the preoperative and the existing levels.

CASE 2 (C. H. No. 205690: adrenogenital syndrome). This 11-year-old girl had an enlarged clitoris shortly after birth. At 6 years pubic and axillary hair and minimal acne of the face and thorax made their appearance. At 8 years of age she was 53 inches tall and weighed 62 pounds. At that time she was seen to be masculine in habitus, although her mother reported that she was feminine in behavior. On physical examination marked acne and well-developed pubic and axillary hair were evident. In the absence of localizing signs an exploratory laparotomy was performed by Dr. Henry W. Hudson, Jr. An essentially normal uterus and normal fallopian tubes were found. The ovaries appeared to be abnormal. Biopsied specimens of both ovaries were examined by Dr. Farber, who reported that there was a developmental disturbance of the follicles but no evidence of testicular tissue. On re-entry, at 11 years of age, the patient weighed 80 pounds and was 55.5 inches tall. The blood pressure was 110/72. Her general appearance had not changed. The skeletal age corresponded with the average normal for 16 years. Dr. Robert E. Gross explored both adrenal glands and found them slightly enlarged. The right gland was removed and examined by Dr. Farber, who found the cortex to be hypertrophied and hyperplastic but free from tumor tissue. Following the operation there was a temporary improvement in the acne, accompanied by a fall in the urinary neutral ketosteroid output to approximately half the preoperative level. Five months postoperatively there was no definite improvement in the clinical status, nor was there any significant difference between the preoperative and existing ketosteroid output.

CASE 3 (Lab. No. 1: probable adrenogenital syndrome). This 7-year-old girl had a profuse growth of pubic hair and a markedly enlarged clitoris. Laparotomy revealed normal ovaries and a slightly underdeveloped uterus. The right adrenal gland was explored and found to be normal in appearance.

CASE 4 (Lab. No. 2: probable adrenogenital syndrome). This 23-year-old woman had pseudohermaphroditic changes which had been present since childhood. At 10 years of age she was excessively tall and had a low voice. At 11 years she became obese. When seen she presented the chief complaints of primary amenorrhea and hirsutism. Her voice was low and she shaved daily. Mild acne was present. She was obese and had abdominal striae. There was no breast development. The pubic hair had a male

distribution. The clitoris was 2 cm. long. There was apparently a rudimentary vagina. A mass was felt in the left upper quadrant. Periadrenal air injections revealed bilaterally enlarged suprarenal bodies.

Case 5 (C. H. No. 231122: probable combined Addison's disease and adrenogenital syndrome). The case of this 2-year-old boy has been described in detail elsewhere.[16] The outstanding findings included macrogenitosomia, hyperpigmentation of the nipples and symptoms indistinguishable from those of Addison's disease. Although the penis was very large for the patient's age, the testes were of infantile size. The skeletal age was advanced to the normal for 4 years of age. Intravenous pyelograms revealed no definite abnormalities of the kidneys. The blood pressure was 95/70. The available evidence suggested that the patient was suffering from an abnormality of the adrenal cortex, characterized by persistence and hyperplasia of the fetal type of cortex and underdevelopment of the adult type of cortex, a condition similar to that described by Wilkins, Fleischmann and Howard.[17]

Case 6 (Lab. No. 3: Cushing's syndrome without adrenal tumor). This 43-year-old housewife had had 3 normal children. Sixteen years previous to examination she began to feel fatigued and depressed and to have headaches. Two years later the weight increased from 118 to 140 pounds. Two years later the face became plethoric and round. During the last 6 years her previously normal menses had occurred at 2 or 3 months' intervals. Five years previously she was given x-ray treatments to the pituitary gland, which relieved the headaches but not the weakness. Shortly afterward ankle edema appeared. In the last 3 or 4 years the weakness had become more marked. On physical examination the patient was obese and plethoric and had abdominal striae. The blood pressure was 130/70. Combined glucose- and insulin-tolerance tests showed increased insulin resistance and a glucose-tolerance curve of the diabetic type. Roentgenograms revealed osteoporosis of the skull, spine and pelvis. The calcium, inorganic phosphorus, cholesterol, nonprotein nitrogen and protein concentrations of the blood serum were normal.

Case 7 (Lab. No. 4: Cushing's syndrome without adrenal tumor). This 26-year-old woman presented obesity, hirsutism, amenorrhea, striae of the skin and headache of 7 years' duration. Two years previously both adrenal glands were explored and found to be normal. X-ray treatment of the pituitary gland was given, with moderately beneficial results. Shortly afterward the patient developed osteoporosis and renal calculi. An insulin-tolerance curve revealed insulin resistance; a combined glucose-insulin test resulted in a rising blood-sugar curve. The basal metabolic rate was –20 per cent. The calcium, inorganic phosphorus, nonprotein nitrogen and protein concentrations of the blood serum were normal.

Case 8 (C. H. No. 236114: masculine precocity associated with adult-sized testes). This 4-year-old boy showed an increased rate of growth and an abnormally large penis and testes at the age of 3. On physical examination he was 43 inches tall and weighed 62 pounds. The blood pressure averaged 100/65. The musculature was exceptionally well developed and the voice was bass. There was a slight growth of pubic hair, but no acne. The penis and testes were of adult size. Examination of the eyegrounds revealed no abnormalities. The visual fields were normal. Encephalography showed normal lateral ventricles and questionable enlargement of the third ventricle. The mammillary bodies appeared to be normal. Intravenous pyelograms disclosed no abnormality. The skeletal age was that of a child of 7½ years.

Case 9 (C. H. No. 219534: carcinoma of the adrenal cortex). This 3-year-old girl showed large genitalia and pubic hair at 12 days of age. Acne appeared at 3 months. At about 1 year the clitoris was abnormally large and the voice was deep. At 2 years the patient's size and strength were strikingly above normal. At 3 years she was 42 inches tall and was of male body build. The facies were heavy, and the skin greasy. She was not obese. There was abundant pubic hair. The clitoris was markedly enlarged and the labia minora resembled a foreskin. A few vaginal epithelial cells were cornified. A mass was palpable over the right kidney. The bones were heavy; osseous development corresponded to that of a 10-year-old child. Intravenous pyelograms showed the upper pole of the right kidney to be depressed. Dr. William E. Ladd operated and removed a large adrenal tumor. Dr. Farber reported that it was a malignant tumor of fetal adrenocortical origin.

Case 10 (Lab. No. 5: carcinoma of the adrenal cortex). This case of a 13-year-old girl has been described by Friedgood.[18]

Correlation of the excretion data (Table 2) and the characterizations of the patients permit the following comments. The patients with apparent adrenocortical hyperplasia (Cases 1, 2, 3, 4 and 5) excreted approximately six times the alpha, beta and total neutral ketosteroids excreted by normal subjects of corresponding age groups. Two patients (Cases 6 and 7) with Cushing's syndrome excreted normal amounts of alpha, beta and total neutral ketosteroids. A four-year-old boy (Case 8) with enlargement of both testes and penis to adult size excreted only slightly more neutral ketosteroids than did normal children of his age. Two patients (Cases 9 and 10) with carcinoma of the adrenal cortex excreted many times the normal amount of total neutral ketosteroids, abnormally high percentages of which were beta ketosteroids.

Discussion

Differences in methods of assay make it impossible to compare directly the data presented above with most of the measurements given in the literature. Even so, a survey of the literature reveals that the relative levels of total neutral ketosteroid excretion by normal children and adults observed here are in general agreement with the findings of other investigators.[19–26] Normal children below seven years of age excrete negligible amounts of hormone. A definite rise in excretion levels which tended to antedate the appearance of secondary sex characteristics was observed in children between seven and twelve years old. The groups of children reported here are too small to permit observations on the differences in rates of excretion of boys and girls.

Butenandt et al.[27] and Callow et al.[2–5] estimated the beta neutral ketosteroid content of pooled male and female urines by an intricate chemical procedure. They reported that the beta ketosteroids (dehydroisoandrosterone) comprised approximately 10 per cent of the total ketosteroids isolated. The data obtained on normal individuals by the relatively simple and directly quantitative colorimetric procedure employed here compare favorably with these reports, and indicate that the beta fractions comprise, on the average, at least 10 to 15 per cent of the total output.

The elevated excretion of neutral ketosteroids by patients with apparent adrenocortical hyperplasia is in keeping with the increase in capon growth-promoting substances observed in similar patients by other workers.[28–30] The fact that unilateral adrenalectomy was followed by only a temporary fall in neutral ketosteroid excretion and remission in the clinical signs of virilism suggests that the operation is without benefit to such patients.

The two patients with Cushing's syndrome and the boy with adult-sized testes and genitalia were essentially normal, with respect both to total output and to the relation of the alpha and beta fractions.

In contrast to the foregoing, the beta ketosteroid content of the urine from the two patients with carcinoma of the adrenal cortex markedly exceeded the normal values. These high values correspond closely to those observed by other investigators,[8–10] who estimated the beta ketosteroid output by isolating dehydroisoandrosterone or isoandrosterone in crystalline form after extensive purification. Furthermore, the remarkably high output observed in these patients is in agreement with those reports in the literature which are based on biological and colorimetric methods of assay.[18, 31, 32]

Although the available evidence indicates that a markedly elevated excretion of beta neutral ketosteroids is diagnostic of adrenocortical carcinoma, our present experience is not sufficiently extensive to permit the conclusion that a normal or slightly elevated output rules out this diagnosis.

Summary and Conclusions

With a relatively simple and directly quantitative colorimetric method for assaying the alpha, beta and total neutral ketosteroid content of twenty-four-hour urine specimens, preliminary data defining the average normal rate of excretion of these substances by children of varying ages and by adult men and women were obtained. The rate of excretion of neutral ketosteroids by patients presenting male sex precocity, virilism or Cushing's syndrome (not associated with carcinoma of the adrenal cortex) has been compared with the aforementioned normal rates of excretion. This comparison leads to the following conclusions:

The beta neutral ketosteroids arise solely from substances produced by the adrenal cortex. It follows as a corollary that the rate of excretion of beta ketosteroids may be an index of at least one aspect of adrenocortical activity.

The assay of the alpha, beta and total neutral ketosteroids gives specific information which may be useful in differentiating adrenocortical hyperplasia, Cushing's syndrome without adrenal tumor, and adrenocortical carcinoma.

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THE RELIABILITY OF THE LEUKOCYTE COUNT IN THE DIAGNOSIS OF APPENDICITIS

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THE significance of the total and differential white-blood-cell counts in appendicitis has been debated for more than a generation without any unanimously accepted conclusions' being reached. It would seem of interest to subject this problem to some sort of statistical analysis, in the hope of securing factual evidence to replace the vague type of clinical impression which governs many surgical decisions at the present time.

The material studied came from the records of the Springfield Hospital and may be divided into two groups. The 50 cases used as controls consisted of benign and noninflammatory lesions such as strabismus, orthopedic deformities, nevi, lipomas and so forth. All these patients were otherwise healthy and free of infection, and all had normal temperatures, except for 1 child with an unexplained admission temperature of 100°F. by mouth, which fell to normal within a few hours. In the second group were 221 cases subjected to laparotomy because appendiceal disease was suspected. These were grouped according to certain arbitrary clinical classifications, which were often the product of retrospective surgical opinion rather than of preoperative diagnosis. The classes were acute appendicitis, acute appendicitis with abscess, acute appendicitis with perforation, acute appendicitis with peritonitis, subacute or chronic appendicitis and mesenteric adenitis. The subacute and chronic cases were grouped because it was found that the distinction between the two represented the purely personal opinion of the surgeon which could not be correlated with the duration of symptoms, physical signs, temperature, white-cell count or gross pathology. The original opinion of the pathologist, Dr. Fred D. Jones, which was based on the gross lesion, was reduced to simplified terms after discussion with him, namely, to normal, inflamed and necrotic appendices. The absence of histological study is hardly a serious omission in the acute cases, as there is probably no hurry about removing an appendix in which the pathologic changes can be demonstrated only by microscopic study. In the case of the so-called "subacute or chronic" cases the surgeon may still comfort himself with the reflection that histological study might have revealed changes justifying operation, although opinions differ as to how much such observations are likely to alter the opinion of a competent pathologist, based on examination of the gross specimen. No attempt will be made in this study to determine the existence of that amorphous entity known as "chronic appendicitis," as adequate follow-up of the operated cases has not been possible. Without denying that many cases of chronic abdominal pain may be permanently relieved by removing a grossly normal appendix, it has also been found that many such cases were subsequently readmitted because of recurrence of the pain.

The classification according to total white-cell count and percentage of polymorphonuclears requires no explanation. The duration of symptoms was included in the hope that it might help to delineate more sharply the cases listed as chronic or subacute appendicitis. But whereas these cases fell into the classification of weeks, months or years to a greater extent than did the cases diagnosed as acute, there was considerable overlapping.

Before attempting to appraise the clinical significance of leukocytosis and elevated polymorphonuclear percentage, it is important to determine the range of normal variations. It is well recognized that this range shifts as the child matures.[1] In this study, however, the operated cases as well as the controls were distributed over age groups in which the adult range of variations may be

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expected. This range is usually regarded as from 5000 to 10,000 for the white-cell count and from 60 to 70 per cent for the polymorphonuclear distribution.[1, 2] An excellent statistical analysis by Medlar,[3] published a decade ago, showed that in an average healthy individual in the course of a few weeks the total white-cell count might vary by 100 per cent and the differential count by 30 per cent without the presence of clinical disease. These variations, moreover, might take place in a given individual in the course of an hour. The least variation encountered was 30 per cent for the total white-cell count and 7 per cent for the polymorphonuclear distribution. Medlar found that a septic leukocyte formula could develop in a normal subject without any clinical evidence of infection. He concluded that the leukocyte mode was 6000 to 9000 for the total white-cell count and 50 to 64 per cent for the polymorphonuclear distribution. In the present study the white-cell count of the control cases was found to have a range from 4300 to 18,600, with a mean of 9286. The standard deviation was ± 3385. This gives a normal range, therefore, of 5901 to 12,671. This so closely approximated the textbook normal of 5000 to 10,000 that it was decided to consider a count of 10,000 or more as constituting a leukocytosis. The polymorphonuclear percentage of the controls ranged from 38 to 87 per cent, with a mean of 65 per cent and a standard deviation of ± 11 per cent. This suggests a normal range of 54 to 76 per cent. It seemed reasonable, therefore, to accept the textbook figure of 70 per cent as the criterion of polymorphonuclear leukocytosis. It is realized that many clinicians consider the total polymorphonuclear count rather than its percentage to be the significant figure. For that reason the cases were also studied in regard to the combination of a total white-cell count of 10,000 or more and a polymorphonuclear percentage of 70 or more. They were similarly studied for the combination of 15,000 or more and 80 per cent or more.

The temperature of 50 control cases showed much less variation, ranging from 97 to 100°F., with a mean of 98.5° and a standard deviation of ± 0.3. It was thought, however, that the temperature should be 100°F. or more before being considered febrile, since the control cases for the most part represented mouth temperatures, whereas the operated cases varied in the technic of registration.

These rather arbitrary standards of normality having been established, it was decided to study each entity in terms of each of the others. The data bearing on the white-cell count and the polymorphonuclear percentage are summarized in Table 1. The complete master table, representing every factor in terms of every other factor, proved to be so cumbersome that it has been omitted for the sake of brevity, and only the pertinent data are included in the following discussion.

The narrow maximum-minimum range of temperature and the small standard deviation in the control group suggested that temperature might be a valuable diagnostic feature, but a study of both clinical and pathological classifications showed very inconstant correlation between temperature and actual severity of the lesion. Of 55 patients classified at operation as having acute appendicitis with abscess or perforation or peritonitis, 22 had normal or subnormal admission temperatures shortly before operation. So also did 63 of the 107 patients whose appendices were classified by the pathologist as acutely inflamed. Conversely, 22 of 113 patients with normal appendices had temperatures ranging from 100 to over 102°F. without any other obvious cause. Nor was there any significant correlation between total and polymorphonuclear leukocytosis and febrile tempera-

TABLE 1. *Total White-Cell Counts and Polymorphonuclear Percentages in All Cases.*

Polymorphonuclear Percentage	No. of Cases	Total White-Cell Count: Under 5000	5000–10,000	10,000–15,000	15,000–20,000	20,000 and over	Unknown
Controls (50 cases)							
Under 50	4	0	3	0	1	0	0
50–60	10	0	8	2	0	0	0
60–70	19	0	14	4	1	0	0
70–80	12	1	6	3	2	0	0
80–90	5	0	2	2	1	0	0
90–100	0	0	0	0	0	0	0
Unknown	0	0	0	0	0	0	0
Totals		1	33	11	5	0	0
Appendices normal according to pathologist (113 cases)							
Under 50	5	0	4	1	0	0	0
50–60	15	1	11	3	0	0	0
60–70	37	0	30	7	0	0	0
70–80	30	0	18	11	1	0	0
80–90	18	0	2	10	6	0	0
90–100	5	0	0	1	3	1	0
Unknown	3	0	0	2	1	0	0
Totals		1	65	35	11	1	0
Appendices inflamed according to pathologist (61 cases)							
Under 50	0	0	0	0	0	0	0
50–60	3	0	3	0	0	0	0
60–70	6	1	5	0	0	0	0
70–80	13	0	10	2	0	1	0
80–90	19	0	2	6	8	3	0
90–100	16	0	0	1	9	6	0
Unknown	4	0	1	1	2	0	0
Totals		1	21	10	19	10	0
Appendices necrotic according to pathologist (46 cases)							
Under 50	0	0	0	0	0	0	0
50–60	0	0	0	0	0	0	0
60–70	2	0	1	1	0	0	0
70–80	3	0	0	2	1	0	0
80–90	20	0	4	5	7	4	0
90–100	14	0	0	3	3	8	0
Unknown	7	0	0	1	2	3	1
Totals		0	5	12	13	15	1

ture. This seems to lend statistical support to the clinical opinion, held by many experienced surgeons, that the thermometer is of little help in the diagnosis of appendicitis.

Chronic appendicitis showed about the same frequency distribution of febrile cases as did the control group. Mesenteric adenitis was indistinguishable from acute appendicitis so far as the incidence of fever was concerned. The 16 cases of this condition were included in the study inasmuch as exploration was undertaken because of suspected appendicitis and the appendix was actually removed in all but 1 case. None of the criteria studied helped to distinguish mesenteric adenitis from appendicitis. Of the 5 patients with polymorphonuclear distributions of 90 to 100 per cent, 2 had acutely inflamed appendices. But of the 2 patients with white-cell counts of over 20,000, one had a normal and the other an acutely inflamed appendix. If we delete these 2 cases of appendicitis, it is evident that mesenteric adenitis may present a clinical picture indistinguishable from appendicitis so far as history, temperature, white-cell count and polymorphonuclear percentage are concerned.

The duration of symptoms was exceedingly variable. They were of comparatively short duration in the cases classified as acute by the surgeon or as actively diseased by the pathologist. This was particularly true of cases with perforation or peritonitis, suggesting that the virulence of the infection, rather than neglect or procrastination, was responsible for these complications. Long duration of symptoms predominated in cases classified clinically as chronic or subacute and in those classified by the pathologist as normal. The two were often synonymous. Of 92 cases classified clinically as chronic or subacute, 79 patients were considered by the pathologist to have had normal appendices. And of a total of 113 cases with normal appendices, 79 were found to have been called subacute or chronic appendicitis, 21 acute appendicitis and 13 mesenteric adenitis at the time of operation.

How closely does the white-cell count parallel the intensity of the pathologic process in the appendix? Of 127 patients who were suspected of having a diseased appendix and who had a white-cell count of 10,000 or more, 79 (62 per cent) had appendices which actually needed removal, as evidenced by the pathologist's diagnosis of acute inflammation or actual necrosis. Of 70 suspects with a leukocytosis of 15,000 or more, 57 (81 per cent) had appendices which needed removal according to the pathologist. Conversely, of 107 patients having appendices with demonstrable gross lesions, 79 (74 per cent) had preoperative white-cell counts of 10,000 or more. Obviously the higher the white-cell count in a case suspected of appendicitis, the greater the chance of finding a definite lesion on exploration. But the percentage chance of deviation from this correlation must be appreciated if one is to avoid serious surgical errors from a blind faith in the reliability of the white-cell count. For example, 29 per cent of the suspected cases with counts below 10,000 had acutely diseased appendices and 10 per cent had necrotic or ruptured appendices. The constancy of this relation may best be measured by a consideration of Table 2. This table also suggests that the differential count is little if any more reliable than the white-cell count as a criterion of either inclusion or exclusion.

TABLE 2. *Correlation of Data.*

CLASSIFICATION	NO. OF CASES	PATHOLOGICAL OR HEMATOLOGICAL FINDING	NO. OF CASES	PER CENT
White blood count of 10,000 or more	127	Diseased appendix	79	62
White blood count of 15,000 or more	70	Diseased appendix	57	81
Diseased appendix	107	White blood count of 10,000 or more	79	74
Normal appendix	113	White blood count of less than 10,000	66	64
White blood count under 10,000	93	Normal appendix	66	71
Polymorphonuclear distribution of 70 per cent or more	139	Diseased appendix	85	61
Polymorphonuclear distribution of 80 per cent or more	93	Diseased appendix	69	74
Diseased appendix	107	Polymorphonuclear distribution of 70 per cent or more	85	79
Normal appendix	113	Polymorphonuclear distribution under 70 per cent	57	55
Polymorphonuclear distribution under 70 per cent	68	Normal appendix	57	84

When we study the cases suspected of appendicitis with a white-cell count of 10,000 or more *and* a polymorphonuclear percentage of 70 or more, we find that 68 per cent actually needed appendectomy. If we raise the standard to a leukocytosis of 15,000 or more *and* a polymorphonuclear percentage of 80 or more, we find that nearly 83 per cent needed operation. This would appear to be an exceedingly helpful correlation, but it must not be overlooked that 33 (29 per cent) of 113 patients with normal appendices had white-cell counts of 10,000 or more and a polymorphonuclear percentage of 70 or more. Conversely, of the 56 cases with both white-cell counts and polymorphonuclear percentages below the critical level of 10,000 and 70, respectively, 10 (17 per cent) were

found at operation to have acutely diseased appendices.

Summary and Conclusions

In only about 60 per cent of 221 cases suspected of having appendicitis was a total white-cell count of 10,000 or more or a polymorphonuclear percentage of 70 or more indicative of the actual appendiceal lesion found at operation. The combination of the two figures showed a 68 per cent correlation with the pathologist's findings. White-cell counts of 15,000 or more or polymorphonuclear percentages of 80 per cent or more were considerably more reliable, but to have demanded such figures as a criterion for operation would have resulted in neglecting a correspondingly greater number of acutely diseased appendices. The same criticism applies to demanding a white-cell count of 15,000 or more *and* a polymorphonuclear percentage of 80 or more. This combination occurred in 83 per cent of the cases with diseased appendices, but also in 9 per cent of the cases found to have normal appendices. This attempt to measure the reliability of the white-cell count in appendicitis in terms of the percentage chances of error should not be construed as vitiating the usefulness of the procedure. Rather it is a plea not to trust blindly to a low white-cell count as conclusive evidence against appendicitis, nor to a high one as overwhelming evidence in favor of operation.

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REPORT ON MEDICAL PROGRESS

CLINICAL NEUROLOGY

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During the past year, a number of important subjects have come to the attention of clinical neurologists or have developed which might be dealt with here, but which have been or will be considered in other progress reports. For example, the use of sulfanilamide and similar preparations has changed our attitude toward intracranial infections, in particular meningitis. Also a consideration of muscle disorders, presented last year, may well be covered in a later report embodying physiological, chemical and clinical advances in this ever-changing field. Subjects of neurosurgical interest have also been covered under a separate heading. The same applies to a large number of diseases and conditions of the nervous system now recommended for vitamin therapy of one form or another. Again, the fundamental consideration of vitamins had better rest with specialists for the present, and clinical advances in this field be reported when the basis for such treatment has become less nebulous. There remain, however, a number of topics of varied interest to the clinical neurologist.

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Law of Denervation

Cannon[1] has amassed evidence from his own experiments and many numerous earlier observations which he sums up under a "law of denervation," expressed as follows: "When in a series of efferent neurones a unit is destroyed, an increased irritability to chemical agents develops in the isolated structure or structures, the effect being maximal in the part directly denervated."

The evidence is most conclusive in connection with the autonomic nervous system, in which denervation of smooth muscle by interrupting its postganglionic, ganglionic or preganglionic supply leads to overreaction. An example cited is the "paradoxical pupillary reflex": if the dilator fibers of the iris are cut the pupil becomes small, but under certain conditions, such as fright or the injection of adrenalin, the pupil not only dilates but does so more than the pupil of the normal eye. Another example, of clinical significance, is the increased sensitivity to adrenalin of blood vessels denervated because of Raynaud's disease. Skeletal muscle is subject to this law. For example, a paralyzed facial muscle may be made to contract by the injection of acetylcholine. Glands

also follow the law, as shown by experiments on the submaxillary and lachrymal glands.

Not only does the law of denervation hold for the peripheral nervous system, but experimental evidence is offered which suggests that a lesion of the spinal cord may also sensitize the appropriate neurones to overactivity. Cannon even postulates a similar situation in the cortex, and asks, "Is it not possible that tumors, and such lesions of the motor area of the cortex as are associated with the name of Hughlings Jackson, may induce instability of the neighboring cortical cells by destroying their connections with other cortical cells?" Cannon's report, based on physiologic evidence, contains numerous suggestions for clinical adaptation in explaining different types of irritability of the nervous system.

Vertebral Veins and Metastasis

Batson[2] offers anatomical evidence to explain routes of infection and tumor metastasis hitherto inexplicable. By means of injections into human cadavers and living monkeys, he showed that veins ordinarily considered as draining into the inferior vena cava also connect with the vertebral veins, and these in turn connect with cerebral sinuses. He believes that this system of vertebral veins forms a by-pass which may under certain conditions, such as coughing, straining and so forth, admit blood directly from the caval system. He thus explains brain metastasis without lung involvement or an open foramen ovale. While I am not qualified to judge of the reliability of the methods employed by Batson, he seems to supply a long-needed anatomical explanation for certain metastases to the brain and spinal cord, hitherto quite unsatisfactorily accounted for.

Hippocampal Herniation

Considerable attention has been given to herniation of the cerebellum into the foramen magnum, with associated flattening of the medulla against the basilar portion of the occipital bone. This is seen especially with tumors in or about the cerebellum, and is a frequent cause of death. Furthermore, when such a hernia is imminent, it is facilitated by lumbar puncture or withdrawal of spinal fluid from any point below.

Herniation of the brain through the tentorium and its effect have received less recognition. This is caused by an expanding lesion above the tentorium which slowly forces the hippocampus of the temporal lobe into the incisura tentorii. In so doing it causes pressure on the midbrain and may cut off the basilar cisternae, resulting in a partial fluid block between the forebrain and the brain stem. As in foraminal herniation, withdrawal of spinal fluid facilitates the incisural herniation. Schwarz and Rosner[3] give the symptomatology of hippocampal herniation as follows: fluctuation in the state of consciousness; anisocoria, with or without dysfunction of the pupillary light reflex; nuchal rigidity; imbalance of extraocular muscles; cardiorespiratory and thermoregulatory disturbances; paradoxical and shifting signs of involvement of the pyramidal tracts; and decerebrate rigidity. These symptoms are best explained by compression of the brain stem, and dislocation of the brain stem was frequently found by these investigators when the herniation was on one side only.

Reid and Cone[4] lay stress on two results of supposedly direct pressure from the hernia. They believe that the dilated and fixed pupil seen in generalized increased intracranial pressure is due to direct pressure on the third nerve as it passes through the incisura. Not only do they argue from clinical evidence alone, but in experimental observations in monkeys they were able to cause dilatation of the ipsilateral pupil with increased extradural pressure and to see the dilatation disappear on reduction of pressure. These authors also noted thrombosis of the occipital lobe on the same side as the hernia, and explain this on the basis of direct hernial pressure on the posterior cerebral artery. In this connection it will be remembered that Leary and others have stressed unilateral dilatation of the pupil as indicative of the side on which subdural hematoma occurs.

Both Schwarz and Rosner and Reid and Cone discuss a mechanical state occurring in elevated cerebral pressure which should be recognized by the neurologist before too late. In dealing with the condition, Fay in his discussion of Schwarz and Rosner's paper states that resection of the tentorium in the neighborhood of the hernia is indicated and in his experience is a satisfactory procedure.

Headache

Pickering[5] analyzes several types of headache, and concludes that stretching of cerebral arteries is the common etiologic factor in headaches caused by histamine, following lumbar puncture, and in hyperpyrexia, migraine, brain tumor and meningitis. In histamine headache the immediate response is a rise in cerebrospinal-fluid pressure, accompanied by a drop in systolic blood pressure and by flushing of the face. The second stage is a drop in fluid pressure and rise in arterial pressure, and it is at this time that the actual headache comes on, lasting approximately eight minutes.

Horton, MacLean and Craig[6] thus describe a type of headache occurring chiefly in middle life:

> . The pain of which the patients complained was limited to one side of the head. It was a constant, excruciating, burning, boring type of pain which involved the eye, the temple, the neck and often the face. It had none of the tic-like qualities of trigeminal neuralgia, and there were no trigger zones. There was frequently marked tenderness on pressure over the branches of the external carotid and common carotid arteries. The bouts of pain appeared and disappeared very quickly. The onset and cessation frequently could be measured in minutes. The duration of the headache varied from fifteen minutes to several hours. In most cases the headache occurred with clock-like regularity, particularly at night, the patients awakening with pain night after night and week after week at a certain hour. Although night pain was characteristic, pain during the waking hours was common. Remissions and exacerbations in many cases occurred spontaneously.

In 25 such cases the typical attack could be reproduced by the subcutaneous injection of 0.3 to 0.5 mg. of histamine. In 20 of these cases the histamine-induced attack could be completely controlled by the intravenous injection of epinephrine and other vasoconstricting agents, and spontaneous attacks could be controlled in a similar manner. The treatment affording relief in 65 cases was the giving of increasing doses of histamine. The dosage began with 0.05 mg. given subcutaneously twice daily for two days; on the third day it was increased to 0.066 mg. and by the fifth day to 0.1 mg., which was administered twice daily for the next two or three weeks. These authors suggest that this type of headache be called "erythromelalgia of the head."

Penfield and McNaughton[7] have been studying the mechanisms of intracranial pain for a number of years and have now published an amplification of their previous reports, covering the anatomical study of the nerve supply of the dura and the clinical experience that corroborates their conclusions. For the clinician it will suffice to state that dural innervation is found especially about the meningeal blood vessels, and that above the posterior fossa the nerve supply comes from the trigeminal nerve on each side. It is of particular interest that the first branch of this nerve is chiefly concerned, supplying the sensitive longitudinal sinus anteriorly through ethmoidal nerves, and posteriorly through a recurrent branch (tentorial nerve) originating as far forward as the cavernous sinus. A number of detailed and carefully checked case reports are chosen to confirm the conclusions as to points of origin and regions of reference of pain of intracranial origin. Here is a radical difference in conception of the pain mechanism as contrasted with that of previous authors. Penfield and McNaughton assert, "Most headaches seem to us to be dural in origin, but under the definition of 'dural' must be included the dural sinuses and the veins tributary to the sinuses in their course across the subarachnoid space from the brain." The response to stimulation of the dura was always pain, whether the stimulus was pressure, traction, heat or electric current. They find the brain itself insensitive, and also the walls of the ventricles, a conclusion contrary to some previous ones. Certain brain cicatrices are painful. The clinical observations agree with the anatomical in stressing the importance of the first branch of the trigeminal nerve as the principal nerve-mediating pain in the head.

Von Storch, Secunda and Krinsky[8] have sought by means of small injections of air by the lumbar route, directed to different places in the ventriculo-subarachnoid system, to estimate points at which headache is produced. Needless to say, the location of the air is checked by x-ray examination. As little as 2 cc. of air, not enough in their opinion to produce pressure change, causes headache, especially when placed in the basilar cisternae. They also conclude that the walls of the lateral ventricles are insensitive to air injection.

The Hypothalamus

Many papers concerning the hypothalamus have appeared in the last few years. A book by Clark et al.[9] and finally a symposium under the aegis of the Association for Research in Nervous and Mental Disease,[10] together with a series of lectures by Dr. Stephen W. Ranson at the Harvard Medical School in the spring of 1940, have brought out many important aspects of this subject.

To the clinician, the anatomy of this small region of the brain above and immediately posterior to the hypophysis is bewildering. It is a phylogenetically ancient area, grossly not circumscribed, but containing six regions, each with two or more nuclear masses. It has a very rich blood supply. Its anatomic connections are numerous and not yet verified, but fiber connections with the infundibular stalk and the hypophysis, and with the thalamus and with the midbrain, are assured.

Physiological differentiation of the nuclear masses and fiber connections is extremely difficult because of the site of the hypothalamus, its small size and the close apposition of its various components. While many functions of the body are disturbed by interference with this region, it is not at all certain that function originates there. But through its connections with other portions of the brain and with glands of internal secretion — in particular the hypophysis — the hypothalamus exerts a control over sympathetic and parasympathetic activities of the body. No other than autonomic function has been suggested. In

reviewing the physiological and clinical evidence, one may formulate two groups of influence attributable to hypothalamic dysfunction: The hypothalamus is of major importance in temperature regulation, regulation of blood pressure, pilomotor response, water metabolism, fat metabolism and sleep; it is of relative importance in sugar metabolism, sexual behavior, gastrointestinal motility and lesions, somatic response, emotions and personality.

Fulton[11] summarizes the clinical syndromes of the hypothalamus as five in number:

> Hypothermia (posterior nuclei); hypersomnia (posterior nuclei and mammillary bodies); the adiposogenital syndrome with disturbed fat and carbohydrate metabolism (tuber cinereum); diabetes insipidus (supraoptic nuclei), generally accompanied by hyperthermia; and autonomic epilepsy caused by tumors, infection or intraventricular drugs, with manifestations varying with the site of the lesion and involving a mixture of sympathetic and parasympathetic actions. The posterior hypothalamus contains predominantly sympathetic representation, in the middle and anterior nuclei predominantly parasympathetic, and the functions integrated clearly involve both systems; but all levels of the hypothalamus are subject to regulation from thalamic, striatal and cortical levels.

Perhaps for the present clinicians should, in the words of Foster Kennedy, consider the hypothalamus as "a neuroglandular instrument in command of vital rhythm."

Erickson[12] defines neurogenic hyperthermia as follows:

> The clinical picture is dramatic. Most striking is the rapid rise of rectal temperature, the relative warmth of the trunk and the icy dryness of the extremities. Venous blotching often appears in non-dependent portions of the skin of the extremities and less frequently in the trunk. Piloerection may be present, and there is complete absence of sweating (anhydrosis). Thus it is evident that heat loss is reduced to a minimum as there is no sweating, and blood flow in the skin of the extremities is greatly reduced. The patient is quiet, practically never agitated, and almost always unconscious.

Neurogenic hyperthermia, according to this writer, usually follows operation in the neighborhood of the hypothalamus within twelve hours. Once it is established, the patient is likely to die, but when its onset is suspected prophylactic measures may be of great value. These measures are directed to causing heat loss through the skin and slowing of the heart rate. Although very high temperatures have been recorded, the diagnosis does not depend on this point, and Erickson considers such temperatures as an indication of poor appreciation of the situation by doctor or nurse.

"Bulgarian Treatment"

The demand for treatment for Parkinson's disease is apparently increasing. Drugs of the atropine series are often of value, sometimes worthless and sometimes toxic. The usual procedure is to try one after another in an attempt to find the best drug or the best combination of drugs for the given case.

For some time the "original Bulgarian belladonna" has been heralded as by far the best drug — especially perhaps because the supply was precarious. Possibly Vollmer[13] has settled the matter for us. He has used various preparations of belladonna in the treatment of the Parkinsonian syndrome, and has analyzed them. He concludes that there is no secret remedy and that success is not dependent on unknown impurities. The original Raeff's Bulgarian root was found not to be duplicated by other Bulgarian roots, and conversely he found some American roots as potent as the original Bulgarian. He therefore postulates a synthetic formula which in his present opinion is best. It consists of 90.2 per cent hyoscyamine hydrobromide, 7.4 per cent atropine sulfate and 2.4 per cent scopolamine hydrobromide. The average daily dose for postencephalitic Parkinson's disease is 3.30 mg., and that for paralysis agitans 1.86 mg.

Ligamenta Flava and Low-Back Pain

Herniation of an intervertebral disk as one cause of low-back pain with sciatic radiation must now be considered as an accepted fact. In operating on such cases it was occasionally noted that a thickened ligamentum flavum accompanied a ruptured disk; and it was not long before an occasional case operated on for herniated disk failed to show this lesion, but did show a thick ligamentum flavum.

This ligament is a paired structure connecting the laminae throughout almost the entire extent of the spine. It contains chiefly yellow elastic tissue and is capable of considerable stretching. The significant fact is that its lateral attachment forms part of the intervertebral foramen; hence enlargement of this ligament from any cause narrows the foramen and impinges on the nerve root. This is especially true of the lumbar region. A thorough investigation of this subject was conducted by Naffziger, Inman and Saunders[14]; they consider hypertrophy of the ligamenta flava as another important cause of so-called "sciatic" pain.

Brown[15] has investigated considerable literature on the subject. The normal thickness as reported is variable, — 2 to 7 mm. (Spurling[16]), 2 to 4 mm. (Dockerty and Love[17]), — with pathological figures of 10 to 16 mm. and 2.5 to 9.5 mm., respectively. It is therefore evident that thickening may be very considerable. Evidence for establishing this thickening on an intrinsic pathological basis is lacking, and the process is generally considered

one of hypertrophy, and the etiology trauma. X-ray studies are negative except where contrast mediums are used, and even with Lipiodol the best interpretation may not discriminate between a ruptured disk and a hypertrophied ligamentum flavum.

It might perhaps be of academic interest to discuss at length the differential diagnosis between these two conditions, for usually the localization is accurately obtained, and operation is directed in the same manner for both conditions. However, it seems possible that without operation the prognosis in the case of a resilient hypertrophied ligament might well be better than in that of a firm, protruded disk.

Wernicke's Encephalopathy

Encephalopathy, originally described in 1881 by Wernicke, has usually been considered as rare. Its etiology has been obscure, although alcohol has been regarded as the exciting agent or at least an accompaniment. Its treatment is unsatisfactory. It has been for years spoken of as polioencephalitis hemorrhagica superior, a term connoting that it is an inflammation of the gray matter of the brain analogous with poliomyelitis. Recent investigations have helped to a better understanding of this condition.

Briefly the disease is characterized by paralysis of various eye muscles, pupillary changes often simulating the Argyll-Robertson type, a reeling gait, disturbances of consciousness and personality changes characteristic of Korsakow's psychosis. Somnolence, tachycardia and disturbances of respiration are frequent. The disease usually runs an acute or subacute course ending in death.

Campbell and Biggart[18] have collected 12 cases proved by autopsy, and have made clinical and pathological observations of great value. Their pathological findings uniformly showed vascular changes in the subcapillaries, mostly in the gray matter, with a predilection for the corpora mammillaria, thalamus, anterior and posterior colliculi and periaqueductal gray matter. The lesions, usually visible to the naked eye, consisted of minute hemorrhages, fragile vessels and a glial reaction. There is no evidence for inflammation, and nerve cells in areas affected remain relatively unaffected. The chief interest of these authors' contribution lies in their discussion of etiology. The cases were all derived from a general hospital, none from mental hospitals, and only 1 was definitely alcoholic. Two patients were pregnant and had vomited, and, most important, 5 had markedly abnormal gastrointestinal tracts (3 gastric carcinoma, 1 an old gastroenterostomy, 1 a bowel resection for tuberculosis). Campbell and Biggart consider the three most likely theories of causation: alcohol, some toxic agent and lack of vitamins. Neither their cases nor most reports in the literature confirm alcohol as a direct cause; the toxic theory, as advanced by Neuburger, does not satisfy them; lack of vitamin B_1 is the only common denominator which to them seems present or probable in their cases; yet they suspect that some other factor, perhaps an endotoxic one, is contributory.

Ecker and Woltman[19] come to a similar conclusion, namely, that there is a deficiency of vitamin B, and perhaps vitamin C, but it must be admitted that the evidence given is not highly satisfactory.

In this connection some experimental work by Alexander, Pijoan and Myerson[20] is contributory. These workers were able to produce the lesions of Wernicke's disease in pigeons by withholding vitamin B_1 but not by withholding vitamin C.

* * *

In closing this review it is fitting to comment on a new textbook on neurology written by the late S. A. Kinnier Wilson.[21] This is a two-volume work representing the ideas of a single great neurologist, except for necessary posthumous editing by A. Nimian Bruce. It thus follows, without superseding, the valuable works of Gowers and Oppenheim.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

ANTEMORTEM AND POSTMORTEM RECORDS AS USED IN WEEKLY CLINICOPATHOLOGICAL EXERCISES

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

CASE 26361

PRESENTATION OF CASE

First Admission. A seventy-one-year-old white married Newfoundland carpenter was admitted complaining of pain in the back.

Two and a half years prior to admission the patient fell from a house a distance of 25 feet landing on his back. He was unconscious for about two hours and remained in bed for a few days, following which he returned to work and felt well except for slight discomfort in the upper dorsal and lower cervical regions of the spine. This discomfort soon disappeared. He continued working and felt normal except that the pain occasionally returned, especially on looking upward, forcing him to stop work for one or two hours. Two months before entry the pain became much worse and gradually increased. He could not lie on either side, and after sleeping for about three hours it was necessary for him to sit up to get relief. The pain was aggravated by almost all movements of the neck. It frequently radiated down both arms. It was worse on coughing and sneezing. For many years he had had "stomach trouble," which consisted of gas and belching but no pain. He used laxatives frequently. There were no chest or urinary symptoms, and he had not lost weight. He had been unusually well all his life prior to the onset of the present illness. His family history was noncontributory.

Physical examination showed a well-developed, thin man who appeared younger than his stated age. Examination of the head was negative. The neck showed no enlarged lymph nodes; the veins were not distended. Examination of the chest was negative. The blood pressure was 140 systolic, 90 diastolic. The abdomen was slightly distended. There were no palpable organs, masses or tenderness. Rectal examination was negative. The back of the spine was tender over the first and second dorsal vertebrae. Movements of the neck caused pain. His strength was normal in both arms. Neurological examination was negative.

The temperature was 97.4°F., the pulse 74, and the respirations 18.

Examination of the urine showed a specific gravity of 1.029, a trace of albumin, no sugar, a rare granular and a few hyaline casts, and an occasional red cell and 3 white cells per high power field. The hemoglobin of the blood was 85 per cent. The serum protein was 7.4 gm. per 100 cc. A sputum examination was negative for acid-fast bacilli. A Bence-Jones protein test showed slight cloudiness by the heat test at 70 to 80°F.

X-ray films of the cervical and upper dorsal spine showed slight narrowing of several of the upper dorsal vertebrae with slightly increased dorsal kyphosis, slight scoliosis and osteoporosis. There was marked spur formation between the fifth and sixth cervical vertebrae. X-ray films of the skull were negative. A gastrointestinal series was negative. X-ray films of the chest showed that the lung fields had a mottled appearance, small areas of dullness outlining the lymphatic structure of almost the entire lung field. The left ventricle was somewhat blunted and slightly prominent; the aorta was tortuous and calcified.

After entry it was found that the patient had a chronic cough which he said was due to "catarrh." A son stated that his father's face had been getting thin; this was attributed to the fact that the patient could not eat anything because of stomach trouble. An orthopedic consultant found that the head and neck showed marked limitation of motion during flexion, extension and rotation. There was no localized tenderness over the cervical vertebrae, and examination of both shoulders was entirely negative for limitation of motion. Examination of the upper-back region showed localized tenderness over the rhomboid muscles and over the fourth and fifth dorsal spinous processes. The tenderness was like that of a myositis. Motions of the spine did not seem to affect this pain appreciably, although the patient stated that holding the shoulders back had a tendency to relieve it somewhat. The patient was discharged on the day of admission to return shortly for further study and treatment.

Final Admission (one month later). Since the last admission the patient had eaten very little and had failed rapidly. No new symptoms had developed except that the cough had become more prominent. It was of a repeated, hacking nature, with little sputum. The spinal pain had decreased in severity.

Physical examination showed the patient to be very uncomfortable, with an almost constant cough and dyspnea. There was slight cyanosis of the lips. He appeared anemic and showed evidence of recent weight loss. Examination of the neck was unchanged. Examination of the chest showed weak breath sounds with coarse and fine rales throughout, more marked on the right. The coarse rales were usually heard best at the end of ex-

piration. No tubular or cavernous breathing was noted. There was dullness over the right lower lung field posteriorly. The heart sounds were of poor quality. A systolic murmur was heard at the apex. The blood pressure was 120 systolic, 70 diastolic. Examination of the abdomen was negative. The extremities were normal. Neurological examination was negative.

The temperature was 100°F., the pulse 80, and the respirations 30.

The urine showed a trace of albumin. A Bence-Jones protein test was negative. The blood showed a red-cell count of 3,830,000 with 70 per cent hemoglobin, and a white-cell count of 14,200 with 84 per cent polymorphonuclears, 12 per cent small lymphocytes and 4 per cent mononuclears. The smear showed moderate achromia; the platelets were increased.

X-ray examination showed moderate hypertrophic changes about the margins of the bodies of the cervical and dorsal vertebrae. The right scapula was definitely abnormal in structure about the glenoid, the appearance suggesting bone destruction with a pathologic fracture.

On the third hospital day the patient suddenly slumped on the stretcher while in the x-ray department. He immediately became cyanotic and moribund. The pulse was weak, although the heart beat remained fairly regular. He did not respond to stimulants and died twenty-five minutes later.

Differential Diagnosis

Dr. Aubrey O. Hampton: I am having some difficulty in finding the pathologic fracture and the bone destruction in the scapula. It may be that I have not the right films, but I assume that it was from this film here that the description was taken. It does look abnormal, but I do not think I should go quite so far as to say there is a fracture. Here, in one of the lateral films, you can see the scapula near the glenoid, and it looks as if there is a round area of destruction. The most marked changes are in the chest and upper dorsal vertebrae. There are wedge-shaped vertebrae at the fifth and ninth dorsal areas. There is no paravertebral tumor. The outlines of the vertebrae are quite smooth. The chest findings are very unusual.

Dr. Earle M. Chapman: There is nothing said about the man's occupation except that he was a carpenter. We do not know whether he was exposed to silica. This is not consistent with silicosis?

Dr. Hampton: No; there is a diffuse process in both lungs without gross enlargement of the hilar markings. The appearance is that of plaque-like areas of density perhaps around the lymphatics and around the bronchi, more like diffuse cancer than anything else, possibly due to fibrosis here on this side, but the lymph nodes were not enlarged.

Dr. Chapman: This man came in again one month after this picture was taken, and the film showed definite signs in the chest, particularly at the right base, of what appears to have been consolidation. There was dullness over the lung field, which might have been due to fluid. This is a puzzling situation, but it seems to me that he must have had a diffuse carcinomatous process to account for his death, which was rather dramatic and, I take it, unexpected. He apparently had diffuse involvement of the bone and bone marrow, leading to stimulation of the marrow. We find that he had an increased number of platelets, an elevated white-cell count and an anemia, and at the second entry, after he had begun to lose weight, he had the signs of a pathologic fracture. The first positive laboratory finding was the report of Bence-Jones protein, yet there was no increase of serum protein and no typical plasma cells in the blood smear. One can frequently find a slight amount of Bence-Jones protein in the urine of patients with carcinoma that involves the bone marrow. He had a large amount of albumin in the urine, and that is difficult to explain. He might have had Bright's disease, but with a specific gravity of 1.029 it seems as though the renal function must have been good. There was an occasional red cell in the urine. The one thing we know is that this man for years had had stomach trouble, — gas and belching, — and again at the second entry we find that his stomach had gone back on him. A son said that the patient could not eat anything and that he had become progressively worse, and yet the gastrointestinal series was negative on the first entry.

Where did this cancer arise? It is going to be extensive in the bone and bone marrow, and also more extensive in the lung than indicated by x-ray study, especially at the right base, possibly with destruction leading to an abscess cavity. Apparently, as a final episode, he must have had a fracture of a cervical vertebra causing cord compression and sudden death. A primary tumor of a vertebra is a possibility; however, there is little to indicate it in the history. He might have had a primary tumor in the stomach that was missed by x-ray. I shall discount it and say it was not there because the gastrointestinal series was negative. It might have come from the liver. It is known that hepatoma metastasizes to bones very extensively. Bolker, Jacobi and Koven* reported

*Bolker, H.; Jacobi, M., and Koven, M. T.: Primary carcinoma of the liver with bone metastasis. *Ann. Int. Med.* 10:1212-1221, 1937.

a series of such cases three years ago, pointing out that pathologic fractures and bone metastases can occur without evidence to indicate a primary hepatoma.

I do not suspect the pancreas as the source of the tumor. We have no record of pain in the lumbar region; the back pain was higher. I doubt that it could have arisen in the lower bowel, because of the absence of any symptoms suggestive of obstruction. Were the kidneys involved? Could it be primary hypernephroma involving one kidney or the other, with no localizing symptoms or signs? We know that primary kidney tumors metastasize freely to the lungs and also to bone.

I can only say that the man had widespread cancer involving the marrow. I think the presence of Bence-Jones protein was due to carcinoma in the marrow and not to multiple myeloma. If I had a choice, I should say, first, that it was primary in the liver, and second, in the kidney.

DR. CHARLES L. SHORT: We saw the patient first in the diagnostic clinic, and he presented a picture much as has been outlined. We suspected he had cancer but were quite unable to demonstrate it. At that time the x-ray films of the spine were interpreted as showing only changes due to degenerative arthritis, and the lesions in the lungs were said to be undoubtedly due to fibrosis. We could not talk the radiologists into making a diagnosis of cancer on the chest plate. When he was re-admitted he looked even more like a patient with cancer. He had gone downhill tremendously, and unfortunately died before the x-ray reports came back — so we still had only a probable diagnosis of cancer.

DR. HAMPTON: The pulmonary findings are unusual for metastatic cancer, but we have seen similar ones, notably in cancer of the pancreas.

CLINICAL DIAGNOSES

Pulmonary fibrosis.
Carcinoma of lung?

DR. CHAPMAN'S DIAGNOSES

Carcinomatosis, with metastases to lung and bone marrow.
Primary liver cancer?

ANATOMICAL DIAGNOSES

Colloid adenocarcinoma of head of pancreas, with metastases to liver, lungs, bronchi, cisterna chyli, lymph nodes and cervical vertebrae.
Tumor emboli, pulmonary arteries.
Obstruction of thoracic duct and cisterna chyli with chylous ascites.
Pulmonary tuberculosis, healed, apical.
Nephritis, chronic vascular.

PATHOLOGICAL DISCUSSION

DR. TRACY B. MALLORY: This man had widespread carcinoma including involvement of several vertebrae and a rather extensive extradural growth in the spinal canal. We did not find any factor definitely to explain the precipitate character of his death. There was no fracture of the cervical vertebrae. On the other hand the intraspinal growth may well have produced pressure on the cervical cord and medulla. The primary source of the tumor was in the pancreas. The head of the pancreas, as you undoubtedly remember, is in two sections, one of which is continuous with the body and tail, and is drained by the duct of Wirsung. The other is intimately attached to it, but has a separate duct. The cancer in this case was limited to the portion of the pancreas drained by the duct of Santorini, which did not enter the papilla of Vater. For that reason no jaundice was present. The cancer was quite small, less than 3 cm. in diameter. The lungs showed mostly metastatic tumor, but there were some areas of fibrosis due to an inactive, almost healed, tuberculosis.

CASE 26362

PRESENTATION OF CASE

A seven-month-old female infant was admitted to the hospital because of vomiting of a few hours' duration.

The patient seemed entirely well the day before admission. She took feedings at normal times and in normal amounts. She slept until 1 a.m. the day of admission, when the mother was awakened by the child "moaning." The infant felt hot, was restless and began to vomit; she vomited on four separate occasions until 6 a.m., when she was able to take an ounce of water without emesis. The child continued to be restless and feverish, and at 8 a.m. a "red mark" appeared under the chin. After two more similar discolorations had developed, the mother called a physician, who advised immediate hospitalization. No diagnosis was given at the time. There had been no cough, convulsions or evident weakness. Two weeks before admission, the child had had a cold with cough lasting five to six days, but since that time she had appeared to be well. She had one stool on the morning of admission, and urination occurred once.

The past history revealed that the infant had been a full-term normally delivered baby; breathing occurred immediately, without artificial respiration. The child was formula fed, and at the time of entry was receiving milk (1 quart), water (4 ounces) and Karo (3 teaspoonfuls); strained vegetables, cod-liver oil and Pablum were taken daily. The child had received no orange juice or other fruit juices, as these had been vigorously refused. She gained in weight normally and was seen in the Well-Baby Clinic on numerous occasions. There had been no prophylactic serum inoculations. The infant had had no previous illnesses. The family history was non-contributory; there were five older siblings, the oldest being fourteen, and none of these had been sick; the parents were living and well.

Physical examination revealed a well-developed and well-nourished infant who lay on its back, rolling slightly from side to side and crying continually. The entire skin was stated as being "amazing." There were large areas of blotchy, reddish-black discoloration that blanched with pressure, and remained thus for many seconds after the finger had been removed. Scattered over the body were numerous, palpable but macular hemorrhagic spots, measuring up to 0.3 cm. in diameter. These areas developed under observation and in the course of two hours, twenty to thirty were counted; they occurred without apparent relation to points of pressure or trauma over the body. Except for the skin lesions and a dusky cyanosis of the mucous membranes of the lips, eyelids and nail beds, the physical examination was negative. There were no purpuric spots in the mouth or pharynx. The throat and tonsils were pale.

The temperature was 102.8°F., the pulse 100, and the respirations 32.

Examination of the blood showed a red-cell count of 3,800,000. A white-cell count was 30,000, with 21 per cent polymorphonuclears, 2 per cent large lymphocytes, 69 per cent small lymphocytes, 2 per cent monocytes and 1 per cent eosinophils. The smear showed normal red cells with very few platelets; there were many disintegrating polymorphonuclear cells. The platelet count was 81,000. A gram stain of the blood smear was negative for intracellular diplococci. The bleeding time was 2 minutes. A lumbar puncture showed normal dynamics, and the spinal fluid contained 300 red cells and 8 white blood cells per cubic millimeter, with a total protein of 14 mg. per 100 cc. and a sugar of 36 mg.

The child quickly failed, and died two hours after admission.

Differential Diagnosis

Dr. Richard C. Tefft: This case presents a picture which is absolutely typical of the Waterhouse–Friederichsen syndrome. Indeed, were it not for the discrepancy of a month in age and a mere matter of a difference in sex, it might well be a description of the original case published by Waterhouse, which gives the syndrome a portion of its name. Because the picture is so typical, the differential diagnosis can be very brief.

Certain drugs can cause symptoms somewhat similar, but aside from the fact that self-administration would be practically impossible in a child of this age, any drug which could cause this picture would have produced symptoms much sooner after ingestion — the baby had been asleep presumably from seven o'clock in the evening until one o'clock in the morning. Scurvy could not produce this picture without a preliminary history of the symptoms of subperiosteal hemorrhage, which are so dramatic, together with blood in the urine and spongy, bleeding gums. Acute leukemia might produce the picture, but while this disease sometimes results in an early fatality, it would not be so fulminating as this was and the red count was altogether too high for a leukemia that had been going on for only several days. In the past, when diagnostic methods were not so far advanced as they are at the present time, fulminating purpuras were described. In all probability most of these were cases similar to the one under consideration and not uncomplicated thrombocytopenic purpura. For an uncomplicated purpura to produce death as rapidly as this, the modus operandi would have to be hemorrhage, which is specifically denied in the history of this case. An overwhelming infection of one sort or another is frequently the cause of sudden death in infancy. It kills as rapidly as this, and indeed, I think there is no doubt that this is one type of overwhelming infection.

The only feature in this case which is not absolutely typical of the Waterhouse–Friederichsen syndrome is the lymphocytosis. Usually there is either a polymorphonuclear leukocytosis or a normal white-cell count — occasionally leukopenia. I think the lymphocytosis in the present case can be explained on the basis of a fulminating infection that overwhelmed the bone marrow. As frequently happens in infancy where the response of the tissues supplying white cells to the blood stream is not so sharply differentiated as it is in adults, the baby unable to supply granulocytes to fight infection does the best he can with lymphocytes.

The Waterhouse–Friederichsen syndrome is

characterized by sudden onset, extraordinary purpuric manifestations, collapse, coma and death. At autopsy in every case, massive hemorrhage into the adrenal glands is found. In the earlier reported cases no definite causative agent emerged. In the last ten years, however, in more than half the cases the meningococcus has been grown from either the blood stream, the petechial spots or both. Occasionally a hemolytic streptococcus or a pneumococcus has been reported. I should expect in this child the very numerous petechial hemorrhages would point to an organism in the blood stream, very probably a meningococcus. These petechial hemorrhages are really small infected thrombi, and the organism frequently can be recovered from them. I believe that except for a positive blood culture and massive hemorrhage into the adrenal glands the autopsy showed little.

A Physician: Was the blood pressure taken in this case?

Dr. Tracy B. Mallory: I think not; the history was very brief.

Dr. Harold L. Higgins: The commonest cause of embolic purpura is meningococcal septicemia ("spotted fever") with the purpuric spots elsewhere, as in the mucous membranes and in the organs. In this case one would expect the hemorrhages to have been in the adrenal glands. I should expect the blood pressure to have been very low. I recall one case with a systolic blood pressure of 40, and another with one of 50. Although this youngster had hemorrhages into the skin, there was no involvement of the meninges. I favor reporting the diagnosis as meningococcal septicemia with purpura and hemorrhage into the adrenal glands, rather than as the Waterhouse–Friederichsen syndrome; the former expresses the clinicopathological condition clearly, the latter calls for acquaintance with a clinical entity that is not so well known.

Dr. Edward F. Bland: What is the source of the emboli?

Dr. Higgins: I look on meningococcal septicemia as being like anthrax. The organisms multiply so massively that they cause blocks of the capillaries. This blockage leads to extrusion of blood into the tissues and to the formation of thrombi in the small veins, the latter being the source of the emboli. I should expect that this child had a massive meningococcal growth from the blood stream.

Clinical Diagnosis

Waterhouse–Friederichsen syndrome.

Dr. Tefft's Diagnoses

Waterhouse–Friederichsen syndrome, with massive hemorrhage into the adrenal glands.
Probable meningococcal septicemia.

Anatomical Diagnoses

Meningococcal septicemia.
Hemorrhage into adrenal glands, bilateral.

Pathological Discussion

Dr. Mallory: The autopsy showed a tremendous number of scattered subcutaneous purpuric spots and massive hemorrhage into both adrenal glands. When one cut across them, the cut surface looked like smooth blood clot and one could not grossly recognize any adrenal tissue. The blood culture showed a growth of meningococcus. We have had, so far as I know, only one other case of this sort in the hospital; from the blood of that case a gram-negative diplococcus was also grown. Although the organism was not an entirely typical meningococcus from the bacteriological point of view I think there can be little doubt of its identity. I am willing to consider both Dr. Tefft and Dr. Higgins correct. The case certainly fits the Waterhouse–Friederichsen syndrome perfectly, and unquestionably the primary underlying trouble was a fulminating meningococcal septicemia. How often that may be the case, I am not aware. At the Children's Hospital I understand that all the cases have shown meningococcal septicemia.

Dr. Tefft: In later years it has been reported in most of the cases where it has been searched for.

Dr. Mallory: It would be a comparatively easy organism to miss. Therefore, I should not take negative reports very seriously unless some other pathogenic organisms, such as staphylococci and pneumococci, had been recovered.

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MEDICAL PREPAREDNESS: PLANS FOR TOTAL WAR

The final phase of medical preparedness — one which is of vital necessity but one for which everyone prays there will be no need — concerns plans for total war.

Each armed unit of 1,000,000 men calls for 7500 physicians, with proportionate numbers of dentists, sanitary engineers, nurses, enlisted men and technicians. In the event of war probably a minimum of 4,000,000 men would be mobilized. This would mean a need for 30,000 physicians, of whom only approximately half are available as members of the medical reserve corps of the U. S. Army and Navy. In other words, the majority of 15,000 physicians and probably an appreciable number of the reserve officers would not be suitable for immediate active duty without additional training. The relatively recent members of the reserve corps and those who plan to volunteer should master some of the administrative and practical problems of military medicine and surgery and thus be prepared before the call comes. Furthermore, up-to-date reviews and abstracts of current papers dealing with these problems should be made available to those who are interested. This can be accomplished by publication either in one of the widely read, existing medical journals or in a new periodical entirely devoted to military medicine and surgery.

Committees composed of qualified experts in the various branches of the medical specialties, particularly as they apply to military medicine and hygiene, should be appointed by a well-informed agency, such as the National Research Council. These committees, in turn, should furnish the Services with whatever recommendations for therapeutic or preventive measures the latter require, should approve the release of abstracts and reviews, and should, where necessary, prepare monographs covering the specialties as they pertain to military affairs.

Plans for general, evacuation and surgical hospitals are already well under way, and nearly sixty such units have been organized by the medical schools and large hospitals throughout the country. Every possible effort should be made to keep these units intact, for the efficiency and precision of a surgical team in an operating room, particularly under the trying conditions of war surgery, depend on experience that can only be acquired by having previously worked together.

Provision for the balance of the personnel necessary for medical care during war has little to do with the medical profession, with one exception. There is already a shortage of well-trained laboratory technicians, and in the event of war, this would become even more acute. Hence, some scheme should be devised whereby those who are interested in this type of work will be able to obtain intensive training.

The final step concerns an adequate supply of surgical instruments and other equipment, of biologic products for the prevention of disease and its treatment, and of various therapeutically im-

portant drugs, particularly those, such as quinine and morphine, that are obtained in their raw states from countries with which commerce, at present, is extremely restricted.

Such plans for total war, together with the other necessary steps in medical preparedness, constitute a vast task for the medical profession. It is, however, one that can, and will, be met, with the aid of governmental agencies, public-health departments of states, cities and towns, the National Research Council and national voluntary organizations interested in health and disease. But in order to start the ball rolling, and rolling at the proper speed and in the right direction, the official appointment of a medical co-ordinator or of a co-ordinating board is of prime importance.

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WILD LIFE UNCONTROLLED

Even early in September the abundance of insect life in New England is apparent. It is already probable that no large-scale poliomyelitis outbreak will occur this year, but the thought of this disease, which may have nothing whatever to do with insect life, is always a reminder of those things which evolve about us, perhaps within our midst, but not well within our control. Some of them are pests, some are menaces, some are merely nuisances. In the last century if the farmer wanted apples he just grew them, but now he must protect his orchards against a variety of parasitic life. To what extent these pests are increasing or how much of their prevalence is due to increasing recognition is difficult to know. There is no doubt that both these changes are taking place, and that our expanding knowledge confronts us with an ever-mounting range of problems.

So far as disease in human beings is concerned, the control of the dog can practically control rabies. But in rural regions the control of the dog, to say nothing of other minor domestic animals, is impossible. If a dog is going to be a dog, or a cat a cat, it will hunt and forage in the country or suburban regions to the point that it will expose itself to those vast reservoirs of wild life for which we cannot provide anything which approaches regulation or even understanding. Skunks, squirrels and snakes; birds, bats and bugs; ticks, toads and turtles; flies, fleas and fish; how near all of these may be!

The control of rats has in the past sufficed to control outbreaks of plague. The first outbreak in San Francisco, in 1900, and the recurrence after the earthquake and fire, in 1907, were both suppressed by systematic efforts to destroy rats and their harborages. The continuation of these efforts has reduced the cases of plague in this country to less than one a year for the past decade, and yet field studies reveal that there has been a gradual extension eastward from the Pacific Coast. From rats the disease infected ground squirrels and other wild rodents, and has now been associated with a wide variety of the wild life of the southwestern states. It is of course more closely associated with the communal habits of their fleas and ticks than with those of the species themselves. Who will undertake the control of the fleas and ticks of the squirrels, wood rats, field mice, prairie dogs and rabbits of the western United States?

The recent appearance of Rocky Mountain spotted fever in New England, as well as the recognition of endemic typhus in the middle southeastern states, and the demonstration that these things can be transmitted by the common varieties of ticks and fleas, with which some of our summer resorts abound, are interesting. The thrills so dramatically associated with far-off expeditions of a medical nature may yet be had in our own back yards.

MEDICAL EPONYM

Dercum's Disease

Francis Xavier Dercum (1856–1931), while instructor in nervous diseases at the University of Pennsylvania, published a case report entitled "A Subcutaneous Connective Tissue Dystrophy of the Arms and Back, Associated with Symptoms Resembling Myxoedema" in the *University Medical Magazine* (**1**: 140–150, 1888). Four years later when he was clinical professor of diseases of the nervous system at Jefferson Medical College, he published a report of "Three Cases of a Hitherto Unclassified Affection Resembling in Its Grosser Aspects Obesity, but Associated with Special Nerv-

ous Symptoms — Adiposis Dolorosa" in the *American Journal of Medical Sciences* (N.S. **104**: 521–535, 1892). In this paper he gave his first account of the disease and coined the name by which it is now known, adiposis dolorosa:

> Evidently the disease is not simple obesity. . . . It would seem, then, that we have here to deal with a connective-tissue dystrophy, a fatty metamorphosis of various stages of completeness, occurring in separate regions, or at best unevenly distributed and associated with symptoms suggestive of an irregular and fugitive irritation of nerve-trunks — possibly a neuritis. . . .
>
> Inasmuch as fatty swelling and pain are the two most prominent features of the disease, I propose for it the name *Adiposis Dolorosa*.

R. W. B.

MASSACHUSETTS MEDICAL SOCIETY

SECTION OF OBSTETRICS AND GYNECOLOGY*

RAYMOND S. TITUS, M.D., *Secretary*
330 Dartmouth Street
Boston

CESAREAN SECTION AND INFLUENZAL PNEUMONIA

Mrs. M. F., a twenty-five-year-old primipara at term, was seen at home on January 24, 1929, with a temperature of 102.2°F., a pulse of 100 and respirations of 30. There were very few definite findings in the chest, and a diagnosis of influenza was made.

The family history was unimportant, as was the patient's past history. Catamenia began at thirteen, were regular with a twenty-eight-day cycle and lasted five days without pain. The last menstrual period began on April 18, 1928, making the expected date of confinement January 25. The prenatal course had been uneventful.

About midnight on January 24 the membranes ruptured, and at 3 a.m., mild labor started. The patient was admitted to the hospital about 8 a.m., at which time she was having moderate five-minute pains. Rectal examination showed that the presenting part was high; there was no dilatation of the cervix. Labor continued throughout the day. At 6 p.m. there was still no dilatation and the cervix was moderately thick. The presenting part was not in the pelvis. Abdominal examination disclosed a vertex presentation. At 8 p.m. a low transverse cervical cesarean section was performed under spinal anesthesia. The immediate operative result was good, and a living male child weighing 7 pounds, 15 ounces, was delivered. At the close of the operation the mother's condition was fair.

The day following operation the patient's abdomen became distended and the respiratory infection was worse. The temperature was 102°F., the pulse 120, and the respirations 28. A medical consultation was held, and a diagnosis of influenzal pneumonia was made. The patient was placed on a pneumonia regime and digitalized. The distention was treated with 1/150 gr. eserine sulfate every four hours for four doses, flaxseed poultices and a rectal tube.

In spite of the above treatment, the distention became worse and the cough increased. On January 31, the sixth postoperative day, a small amount of pus was draining from the operative incision. On the following day it was noted that the incision had separated and that a loop of intestine protruded. A surgical consultation was held, and immediate repair advised. The wound was resutured under spinal anesthesia.

For ten days following this second operation the patient's temperature fluctuated between 104 and 100°F. On February 9 the chest condition had cleared, and on February 12 the temperature dropped to normal, where it remained until discharge on March 4.

Comment. This patient was a very sick woman — labor, cesarean section, influenzal pneumonia, wound sepsis. That she recovered speaks worlds of praise for the care which she received. Spinal anesthesia was undoubtedly the ideal anesthetic for the cesarean section, which was necessary to ensure a live baby. The unusual complication of sepsis of the wound with extrusion of a loop of bowel was attacked immediately, and fortunately the result was successful. The patient owes much to the care she received.

*A series of selected case histories by members of the section will be published weekly. Comments and questions by subscribers are solicited and will be discussed by members of the section.

CORRESPONDENCE

PLANS FOR BUDGETING THE COSTS OF MEDICAL CARE

To the Editor: This letter concerning group health services in Massachusetts is written in order to clarify a subject that may still be confused and to indicate some comparisons and suggestions that may lead to constructive thought and action. I have learned of the confusion of thought concerning the White Cross Health Service through having had the privilege of several conferences with members of Medical and Surgical Associates and then finding among physicians opinions about the operation and purposes of this plan at variance with my own impression. Because this difference of opinion seems to me to rest principally on misunderstanding or lack of understanding and because considerable time has elapsed since information concerning the White Cross has appeared in the *Journal*, it may be in order to present the viewpoint of a practitioner not associated with the plan. In order to avoid inaccuracies in dealing with this subject, the facts and purposes pertaining to the operation of the White Cross that appear in this letter have been set forth by one of the members of Medical and Surgical Associates.

The present interest in and growth of group health services are due primarily to recent advances in medical knowledge. These advances are largely responsible for the increased effectiveness of preventive medicine and medical therapy. The resulting decrease in mortality and morbidity rates has made the budgeting of health services practical. The medical profession, the public-health service, the daily press, radio, movies and, last but not least, the personal experience of individuals have taught the public much about "modern medicine." But much health education remains for the future. Because of lack of understanding of how to obtain medical care and budget its cost, good medicine, as differentiated from poor medicine, is not being financed voluntarily by the public so adequately as it should be. Too much money is being wasted on quack remedies and cults. Too many people find that they are unable to pay the costs of good medical care when they are faced with the burdens of illness. Persons with family incomes as high as $30 to $40 per week are admitted to our hospitals as charity patients. The Senate Committee to consider the Wagner Health Bill concluded that, under existing medical practice, families with incomes as high as $3000 or more per year are frequently unable to meet the costs of serious illness.

Several years ago the American Hospital Association encouraged the establishment of hospital-service corporations to facilitate and increase the utilization of hospitals by the public. Most of these services have been carefully controlled and managed. They are enabling subscribers unfortunate enough to suffer serious illness to obtain good hospital care without excessive expense; they permit members in good health to enjoy for relatively little cost the knowledge that they too may receive such care when the need arises; they increase the subscribers' financial ability to pay for their professional medical care; and finally, they not only are augmenting the utilization of hospitals by paying patients, but also are obtaining voluntary financial support from large sections of the public.

Thus, the American Hospital Association has readjusted hospital service to the demands that advances in medicine placed on it. The medical profession needs, likewise, to readjust medical practice to the advances in medical knowledge if it and the public are to profit by them. Practical common sense, not welfare sentimentality, suggests some readjustment in order to finance good medicine, which today means expensive medicine and good doctors adequately remunerated.

During the past two years two steps have been taken in Massachusetts toward such adjustment of our medical services.

In April, 1939, the Massachusetts Medical Society recognized the desirability of providing an opportunity for the public to budget voluntarily the costs of professional medical care. During the course of the year the Society arrived at certain conclusions concerning a service which the Society itself proposes to establish and operate. These may be outlined as follows: first, that the necessity of a cash reserve to cover the liabilities of the service requires operation of the service as an insurance business under the laws and supervision of the Commonwealth pertaining to such business; second, that an enabling act should be obtained from the legislature; third, that this proposed service should grant to any subscriber the right to choose any physician for medical care.

While the Society was evolving these principles, a lay group, known as Health Service, Incorporated (White Cross), obtained a charter to establish a non-profit health service. This service then entered into a contract with a medical partnership for the provision of medical care to White Cross members in the vicinity of Boston. The preliminary drafts of this contract and the agreement between the White Cross and its subscribing members were placed before the profession by publication in the *Journal*. Since then the White Cross has made it clear that this medical partnership is not to have a monopoly of the medical care under this health service. The White Cross desires, with the advice of an advisory council of physicians, to enter into agreements with other groups of physicians for the provision of medical care to subscribing members in other communities.

Through these agreements with such groups of physicians, provision is made for the medical care of White Cross members to be entirely in the hands of qualified physicians. It is pointed out that contracts are made with recognized groups of physicians in order to have an administrative unit for the medical services of each geographical group of subscribers. This, the White Cross believes, is essential to efficient operation of the service. If a single medical group formed the only administrative unit, its administrative functions might become too large and the local needs and facilities might not be wisely met and utilized. The danger of these administrative groups of physicians arbitrarily restricting the physicians participating in the medical care is prevented by the freedom given members in choosing their physicians. Subscribing members may choose as their family physician or family pediatrician any physician who has graduated from a Grade A medical school, is on the staff or courtesy staff of an approved hospital in the community in which he practices, and agrees to be an associated physician of the group of physicians providing medical care to subscribing members. A White Cross member and his associated family physician may then call in any specialist or consultant who is qualified as such by a medical board of certification. Thus, qualifications already established by the medical profession through existing medical societies define the eligibility of physicians. Judgment by administrating physicians is avoided, yet necessary provision is made for protecting the standards of efficient operation of the service. At the same time subscribers are given freedom of choice of physicians within the broad limitations of these qualifications.

Thus, it would seem that the service in a very conservative manner is built around the family practitioner. The personal relation between physician and patient is perhaps more protected than under existing private practice because continuity of the relation between doctor and patient will be encouraged. The family physician is coordinated with accredited specialists who are on the staffs of the well-equipped hospitals of the community. Thus, without disturbing the family physician or specialist in his private practice this service simply, but rather admirably, organizes and utilizes the medical knowledge and facilities of a given community.

The details of the Society's plan have not so far as I know been worked out. How long a time will be required before this can be done, before finances are provided, and before the plan is put into operation is still unknown. The White Cross operating on the simpler and less extensive basis has within the past nine months worked out the details and become in its small conservative way a going concern. It has been investigated by one of the foundations interested in matters pertaining to health and has received financial support from this foundation and from individual residents of Massachusetts. As the public becomes aware of the opportunity to subscribe to this service, which is organized to provide an excellent quality of medical care, the membership should increase. Provision is made for subscribing either as members of employed groups (as is done under the Blue Cross) or as individuals. A high percentage enrollment from a group should be required in order to secure a cross section of health. To

obtain desirable percentages, considerable contact must be provided between prospective subscribers and the White Cross. The details of the service will have to be described and discussed with the interested groups. This essential contact and discussion should be accomplished without transgressing professional ethics. In this connection, it is of interest to note the provisions for observing ethical conduct in accepting individual members. Individuals may become members under somewhat higher subscription rates and upon condition that their acceptance will be dependent on passing a physical examination and their obtaining a statement from any physician treating an existing ailment that payments and obligations have been satisfactorily discharged.

There seems little in the White Cross plan that is not conservative and does not meet the criteria of fair and desirable competition and ethical conduct.

In comparing the Society's projected plan and the White Cross service, the following differences are clearly apparent:

The former is an insurance service. It must, therefore, carry the legally required cash reserves. This complicates its structure and operation and may increase its operating costs. The latter is a health service whose obligation is a service and is, therefore, free from a cash liability that requires legal insurance reserves.

The Society's plan permits complete freedom of choice of physician and in so doing does not protect the average subscriber or average participating physician from the inefficiency and the costs of poor medicine. With about 2000 licensed physicians in the Commonwealth who are not members of the Massachusetts Medical Society and many of whom are graduates of medical schools that are disapproved of by the Society, the maintenance under the Society's free-choice plan of a quality of medicine that permits efficient operation will be difficult. The White Cross plan permits freedom of choice of physician by subscribers from among those physicians who meet certain qualifications already established by the medical profession. This limitation of choice protects both the subscriber and the participating physician. It is a conservative measure which should facilitate the successful operation of the service.

There seems to be little reason for conflict between these two services. The lessons learned by the one should be helpful to the other. Competition between the two is desirable and not dangerous to the profession as the medical service and standards under each are controlled by the profession. It is to the interest of physicians that both services succeed. The failure of either can result only in loss to the profession. For they are both an attempt to extend voluntarily-supported medicine of a good quality.

The White Cross plan appears to be of particular interest as a conservative experiment in budgeted health service that lays particular emphasis on protecting the quality of medical care. Believing that it should be supported by the medical profession as an experiment from which much benefit to the public and the profession may be derived, I wish, in the hope of contributing to its success, to submit the following three suggestions:

That the White Cross establish a council of physicians to advise it concerning the selection of administrative groups of physicians in the various localities where there are subscribing members. The physicians comprising this council should be respected physicians who preferably are not members of any administrative group of physicians associated with the service.

That, as soon as practical, the members of administrative groups of physicians be physicians actively engaged in the practice of medicine. In this connection there has been some criticism of the present personnel of Medical and Surgical Associates. It should be appreciated, however, that the initiative in starting the medical service under this plan could hardly have been undertaken by many practitioners. Now that the service is operating, the desirability of having it controlled by practitioners seems clear.

That the single-income limit of eligibility of subscribing members be modified to provide a shifting scale based on size and financial obligations of the family. In considering this limit, it must be recognized that this is a self-supporting service; that the membership dues must be adequate to provide fair remuneration of the participating physicians; and that, therefore, limits must not be set which will restrict membership to an income level in which individuals cannot afford the necessary subscription rates.

Provision of health services to those individuals who cannot afford such payments as will make a service self-supporting is a different matter. Since the provision of such health services will probably involve the use of tax funds, their consideration should be entirely separate from discussions pertaining to voluntary self-supporting services, such as the White Cross. Let us hope that such experiments as the White Cross or the Society's plan will enable us to cope successfully at a later time with this other problem.

WALTER P. BOWERS, M.D.

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Clinton, Massachusetts.

NOTICES

ANNOUNCEMENT

JAMES HARRISON, M.D., announces the removal of his office from 120 Needham Street, Dedham, to 57 Bridge Street, Dedham.

NEW ENGLAND DERMATOLOGICAL SOCIETY

The next regular meeting of the New England Dermatological Society will be held at the Massachusetts General Hospital, Skin Out Patient Department, on Wednesday, October 9, at 2:00 p.m.

SOCIETY MEETINGS AND CONFERENCES

SEPTEMBER 12–MAY 8 — Pentucket Association of Physicians. Page 263, issue of August 15.

SEPTEMBER 16 — New England Society of Anesthesiology. Page 305, issue of August 22.

SEPTEMBER 16–20 — American Occupational Therapy Association. Page 263, issue of August 15.

SEPTEMBER 17–19 — Clinical Congress of the Connecticut State Medical Society. Page 305, issue of August 22.

SEPTEMBER 27, 28 — New England Surgical Society. Poland Spring, Maine.

OCTOBER 6–11 — Annual meeting of the American Academy of Ophthalmology and Otolaryngology. Page 81, issue of July 11.

OCTOBER 8–11 — American Public Health Association. Page 655, issue of April 11.

OCTOBER 9 — New England Dermatological Society. Notice above.

OCTOBER 11, 12 — Pan-American Congress of Ophthalmology. Page 898, issue of May 23.

OCTOBER 14–25 — 1940 Graduate Fortnight of the New York Academy of Medicine. Page 305, issue of August 22.

OCTOBER 21 — American Board of Internal Medicine. Page 369, issue of February 29.

JANUARY 4, 1941 — American Board of Obstetrics and Gynecology. Page 1064, issue of June 20.

MARCH 8 — American Board of Ophthalmology. Page 201, issue of August 1.

APRIL 21–25 — American College of Physicians. Page 1065, issue of June 20.

DISTRICT MEDICAL SOCIETY

SUFFOLK

NOVEMBER 7 — Censors' meeting. Page 305, issue of August 22.